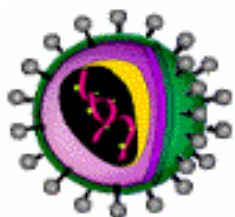


DAIDS Clinical Research Priorities



2006 - 2013



**AIDS Research Advisory Committee &
AIDS Subcommittee, National Advisory
Allergy and Infectious Diseases Council**
May 24, 2004

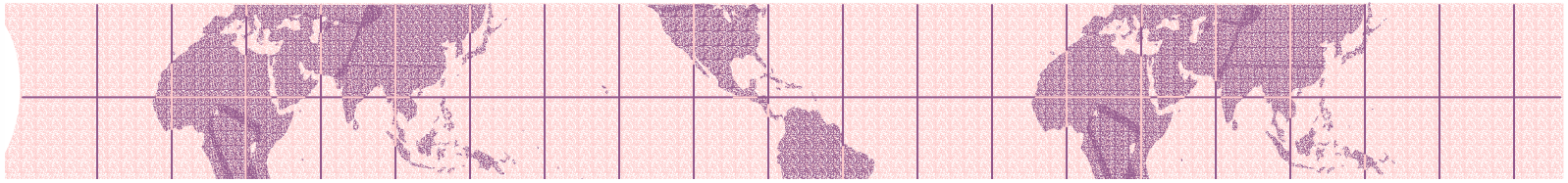
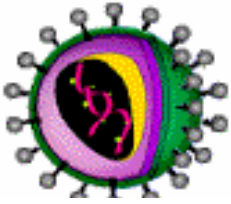


Important Considerations

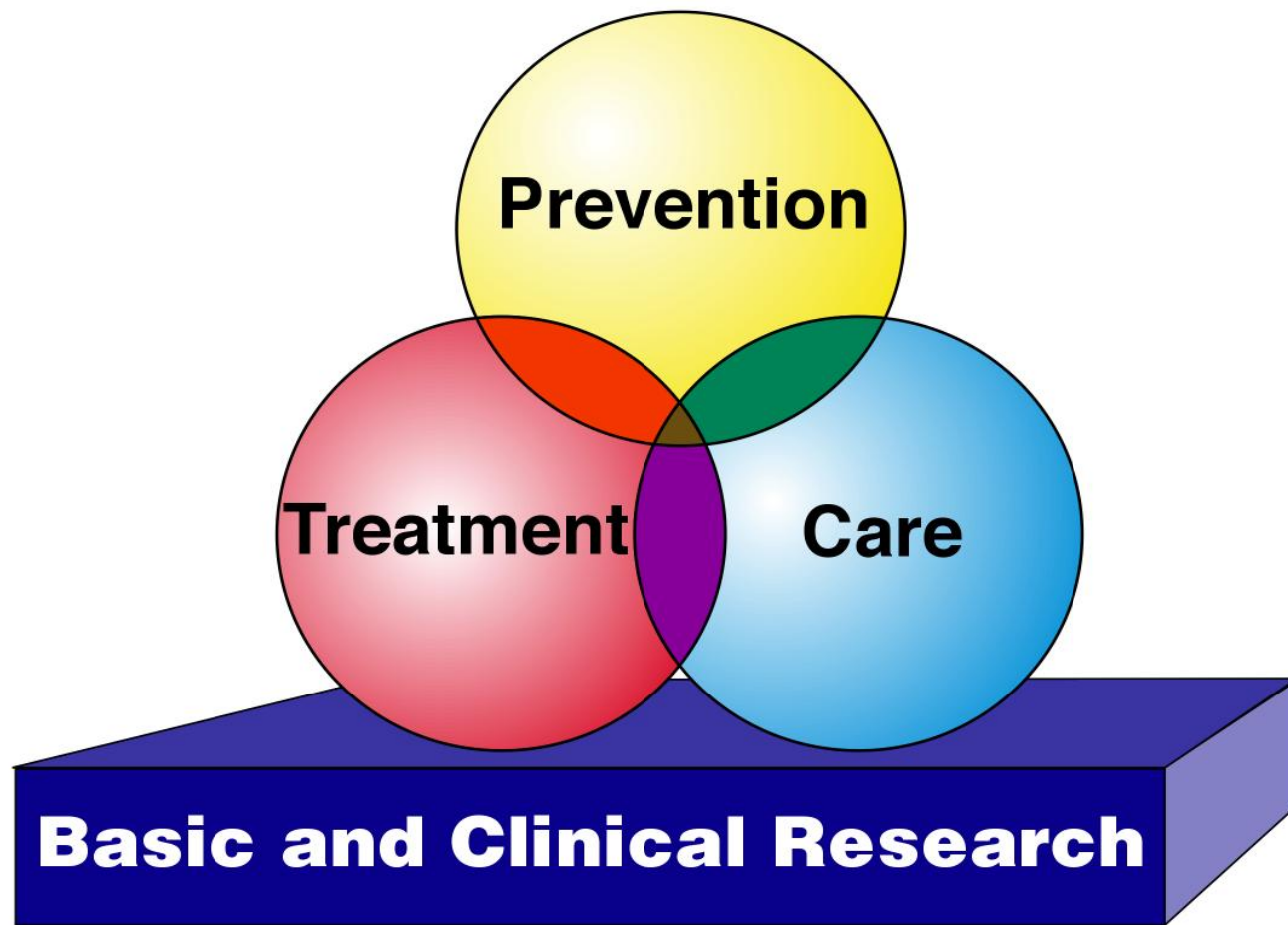
- **Patient Populations**
 - Women, minorities, children, adolescents, families
 - Individuals with co-morbidities
- **Delivery of care or research informing care**
- **Domestic agendas versus international agendas**
- **Competing priorities between scientific areas of emphasis**

- **Focus: Research**





Confronting AIDS in the 21st Century



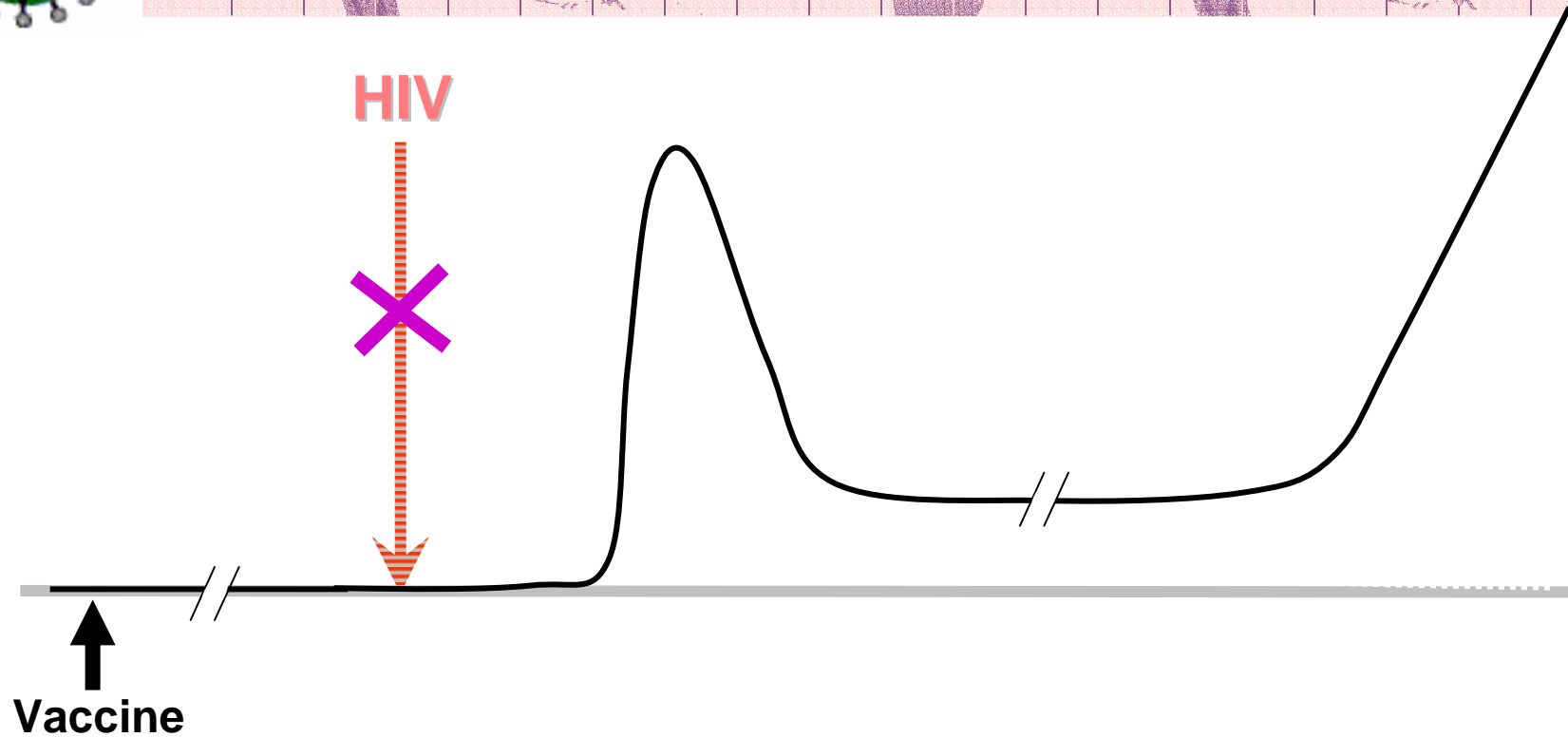


DAIDS Mission: Help Stop the HIV/AIDS Epidemic



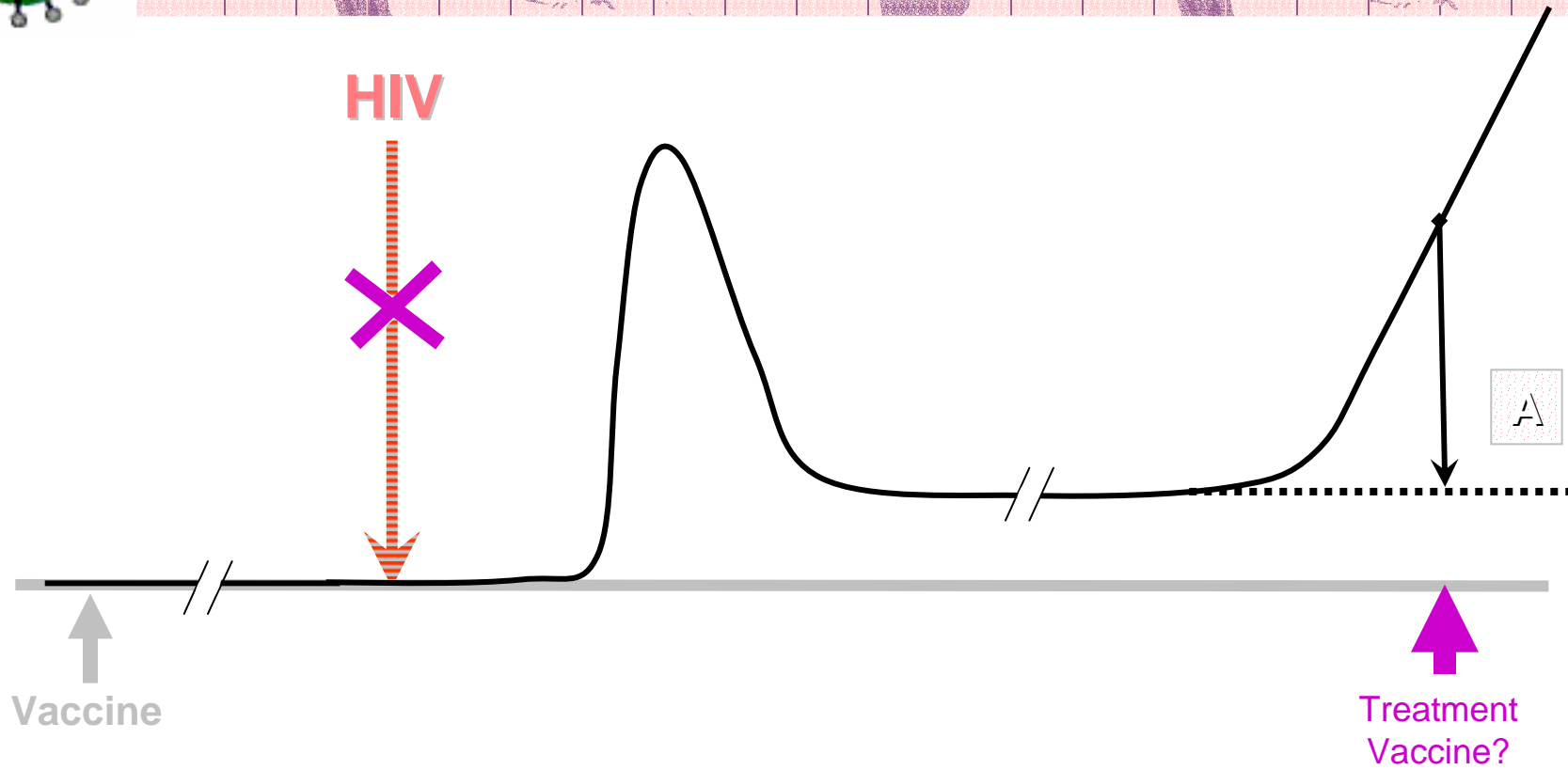


DAIDS Mission: Help Stop the HIV/AIDS Epidemic





DAIDS Mission: Help Stop the HIV/AIDS Epidemic



**A. Stop Progression,
Development of Resistance**



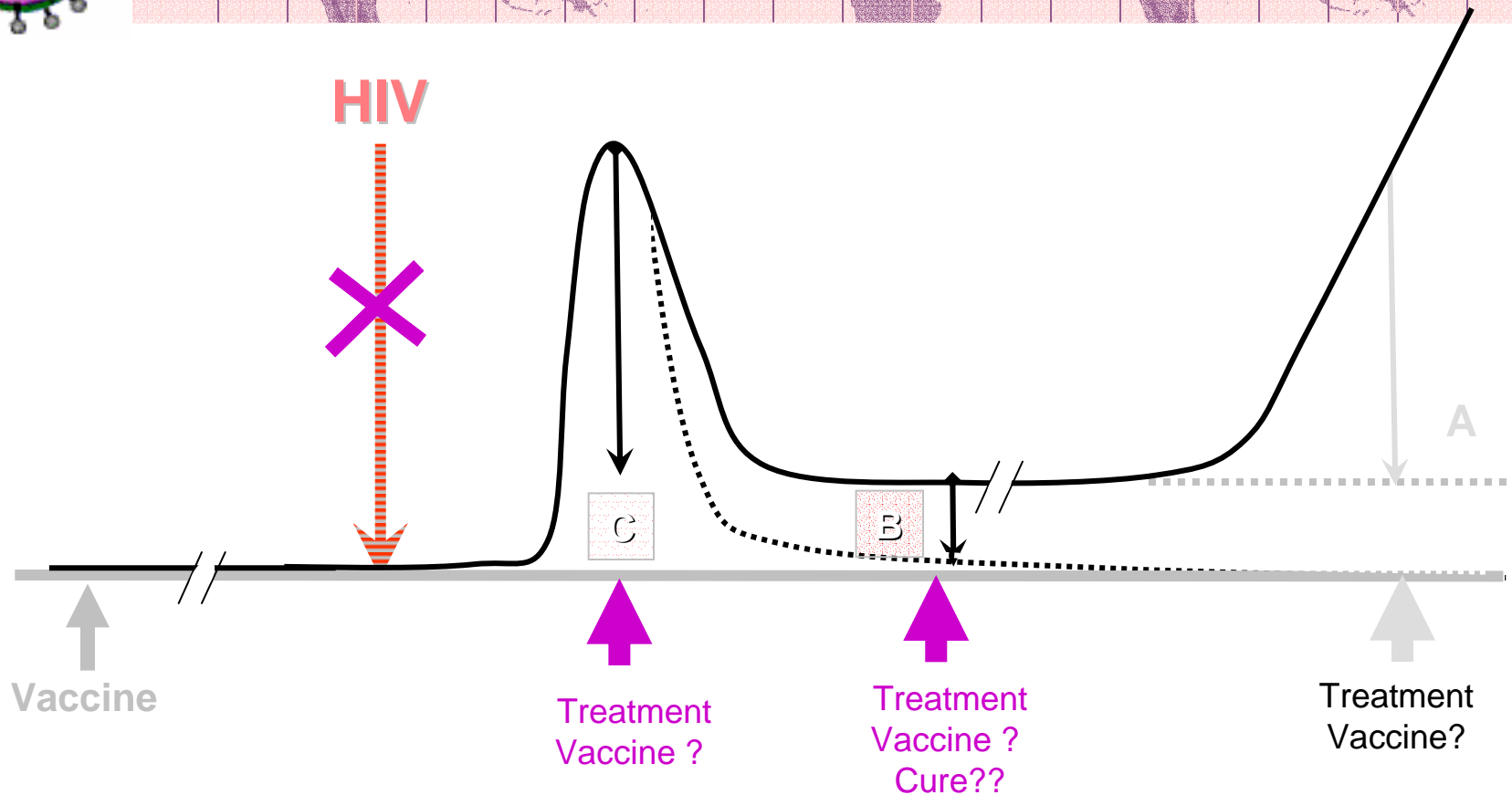
DHHS/NIH/NIAID/DAIDS

ARAC 5-24-04





DAIDS Mission: Help Stop the HIV/AIDS Epidemic



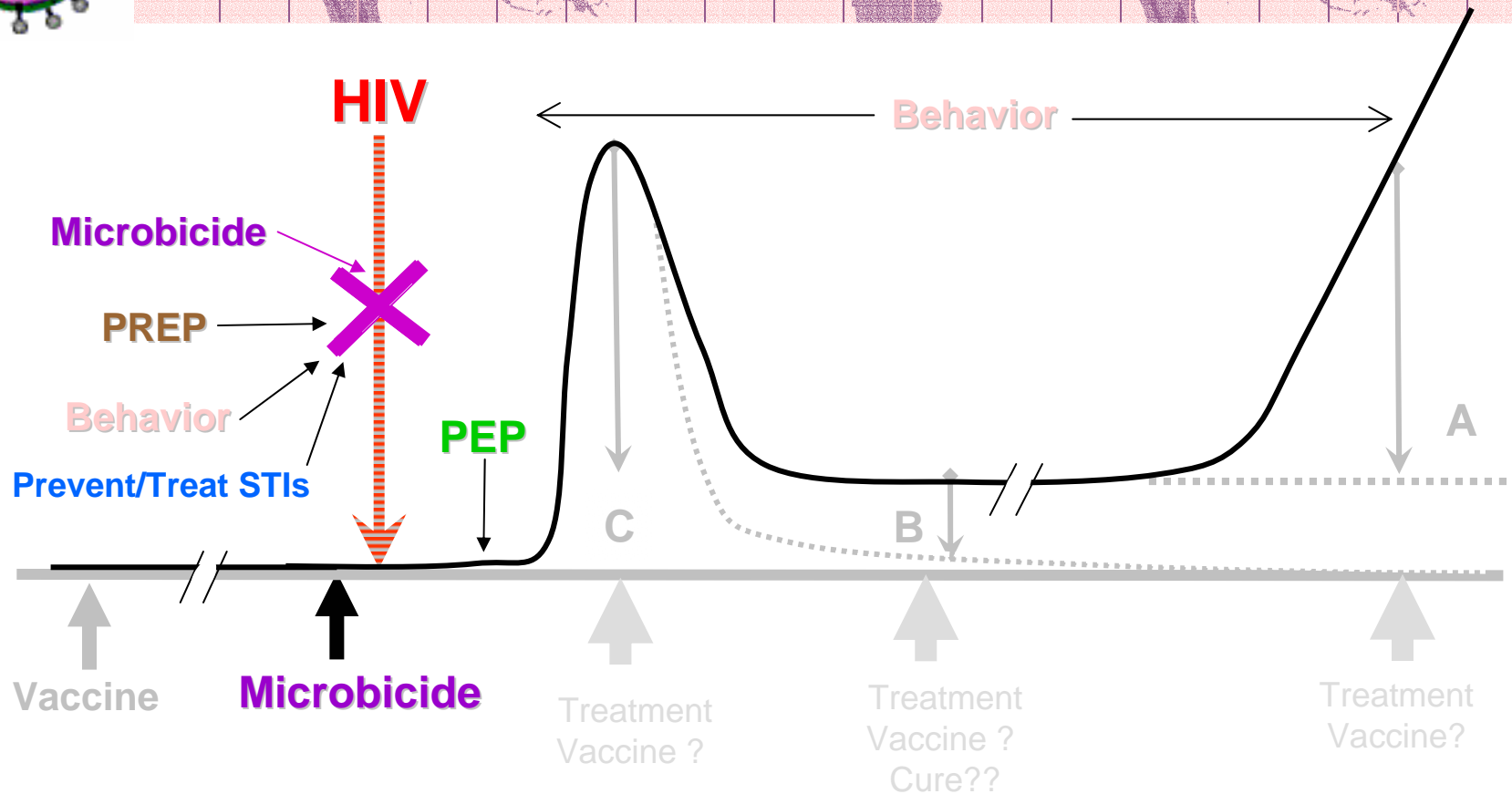
B. Lower Set Point or Eliminate HIV

C. Lower Initial Peak of Viremia

A. Stop Progression, Development of Resistance



DAIDS Mission: Help Stop the HIV/AIDS Epidemic



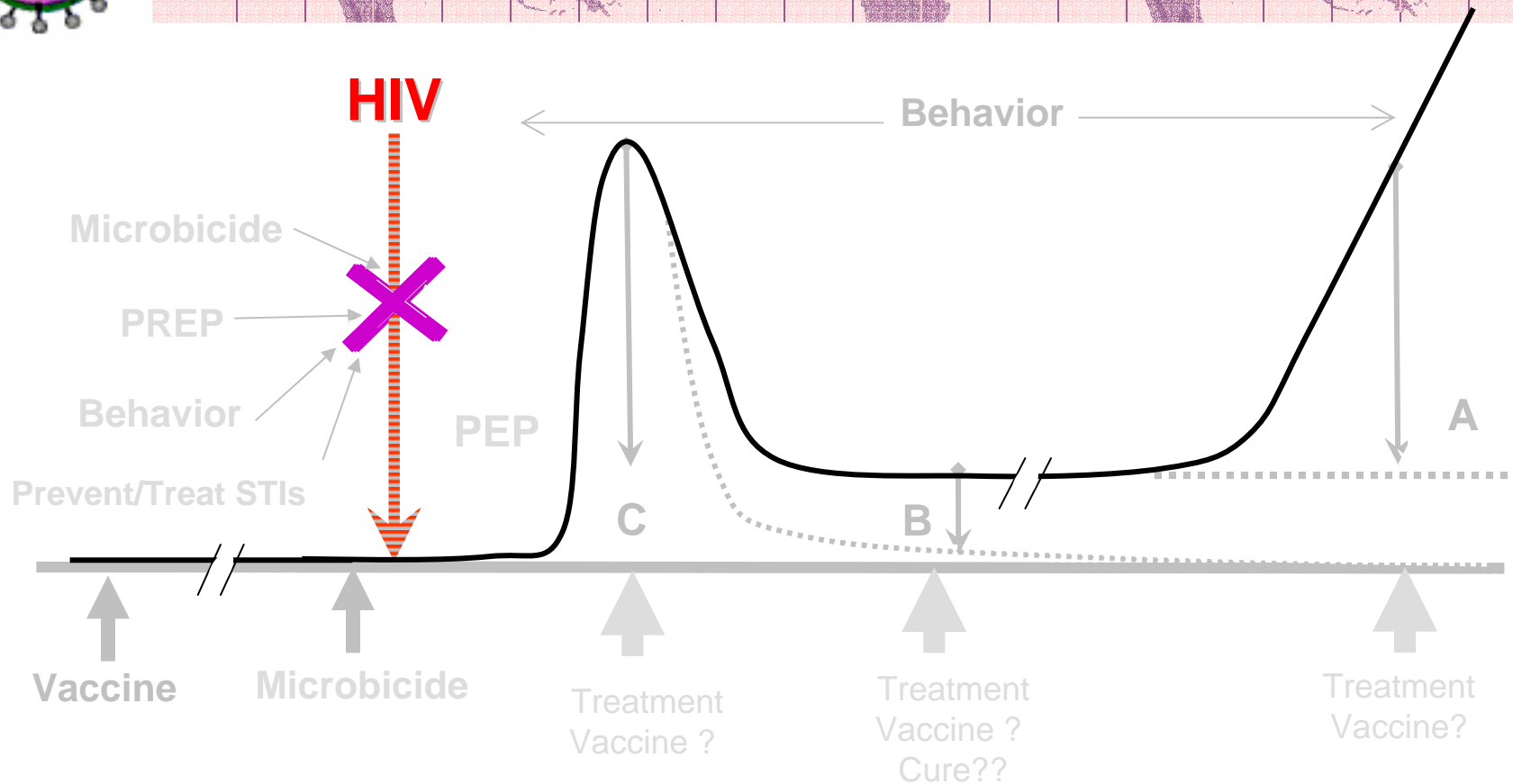
A. Stop Progression, Development of Resistance

B. Lower Set Point or Eliminate HIV

C. Lower Initial Peak of Viremia



DAIDS Mission: Help Stop the HIV/AIDS Epidemic



Populations: Adults
Infants
Children
Adolescents

- A. Stop Progression, Development of Resistance
- B. Lower Set Point or Eliminate HIV
- C. Lower Initial Peak of Viremia



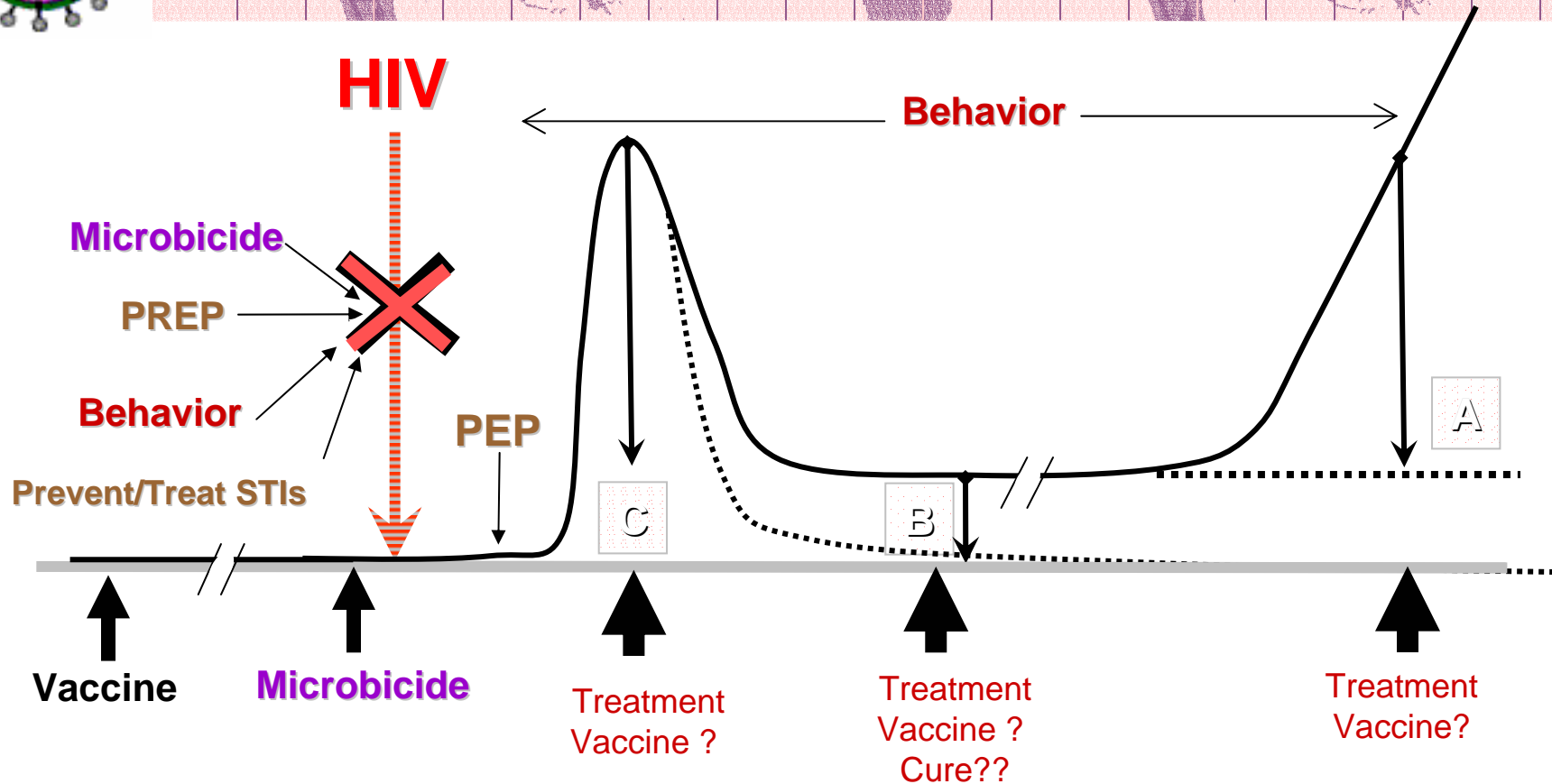
DHHS/NIH/DAIDS

ARAC 5-24-04





DAIDS Mission: Help Stop the HIV/AIDS Epidemic



Populations: Adults ←
Infants ↔
Children ←
Adolescents

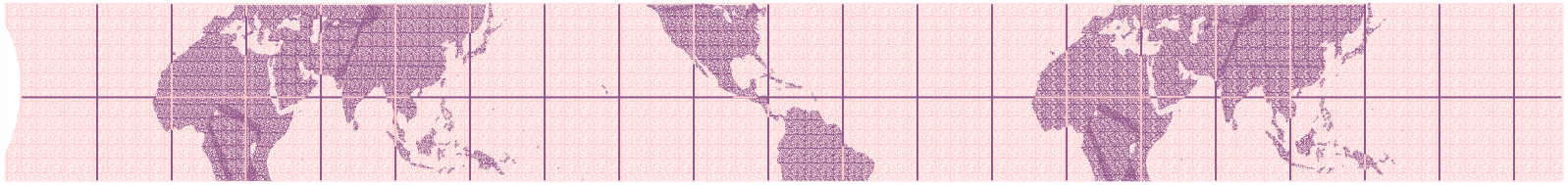
- A.** Stop Progression, Development of Resistance
- B.** Lower Set Point or Eliminate HIV
- C.** Lower Initial Peak of Viremia



DHHS/NIH/NIH/DAIDS

ARAC 5-24-04

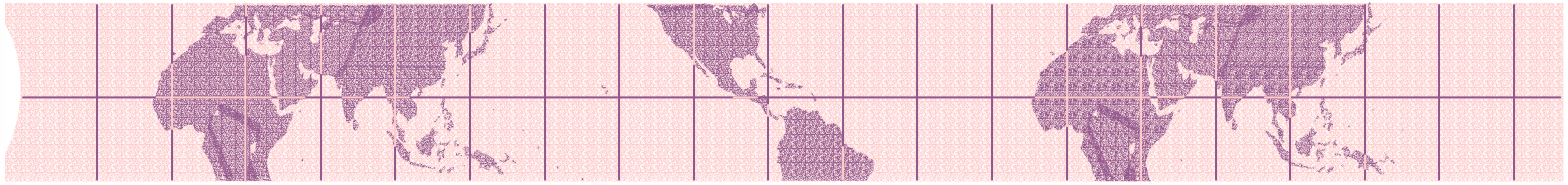




HIV/AIDS Clinical Research Networks-Priority Areas

- **Vaccine research and development**
- **Therapeutics - translational research/ drug development**
- **Therapeutics - optimization of clinical management**
- **Microbicide research and development**
- **Prevention of maternal-child transmission**
- **Prevention research**

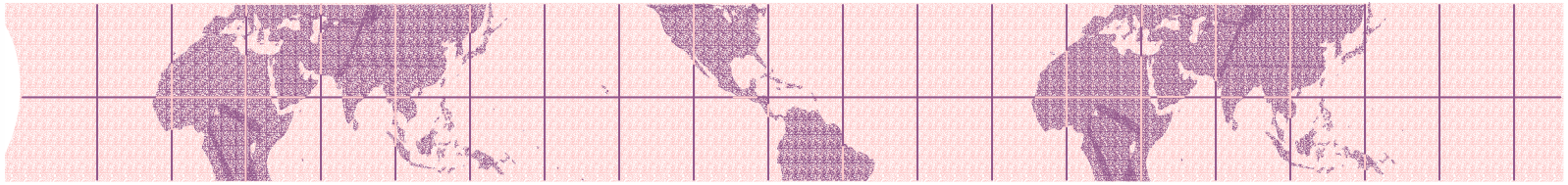




Clinical Research: Overarching Principles

- Identify underserved or disenfranchised populations (e.g. women, minorities, adolescents, young children)
- Specify barriers to participation in clinical research for these and other special populations
- Develop strategies to address the problems identified above

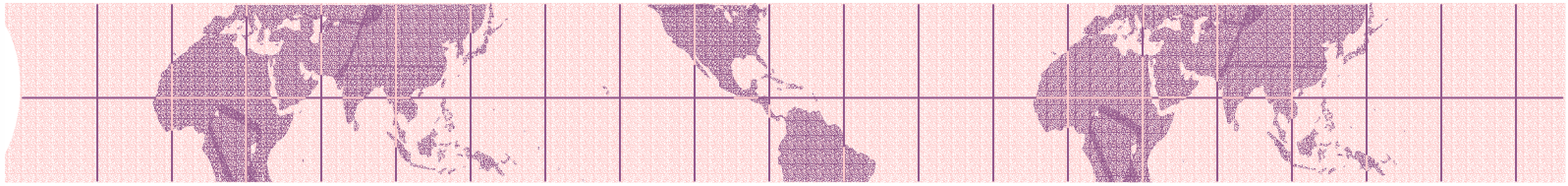




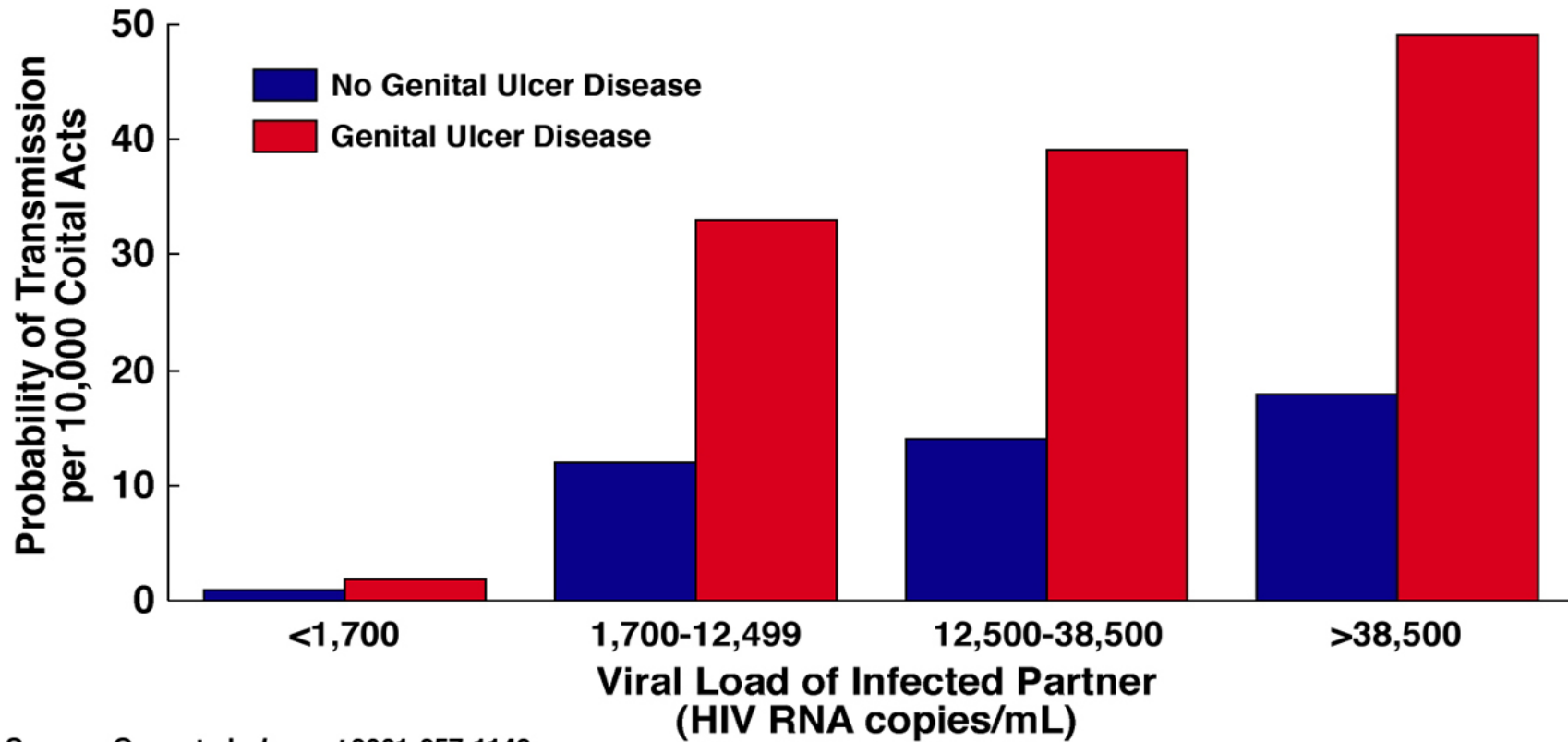
Transmission

- **Role of viral load**
 - **Transmission probabilities per act by quartiles of viral load**
- **Properties of the transmitted viruses in a cohort of Clade C infected discordant couples**
- **Timing of transmission**

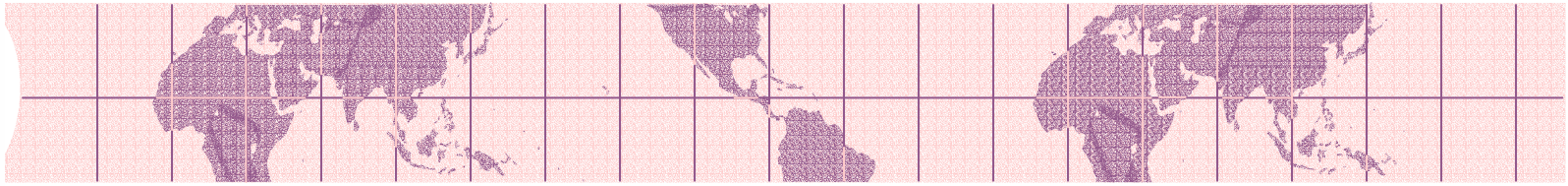




Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda

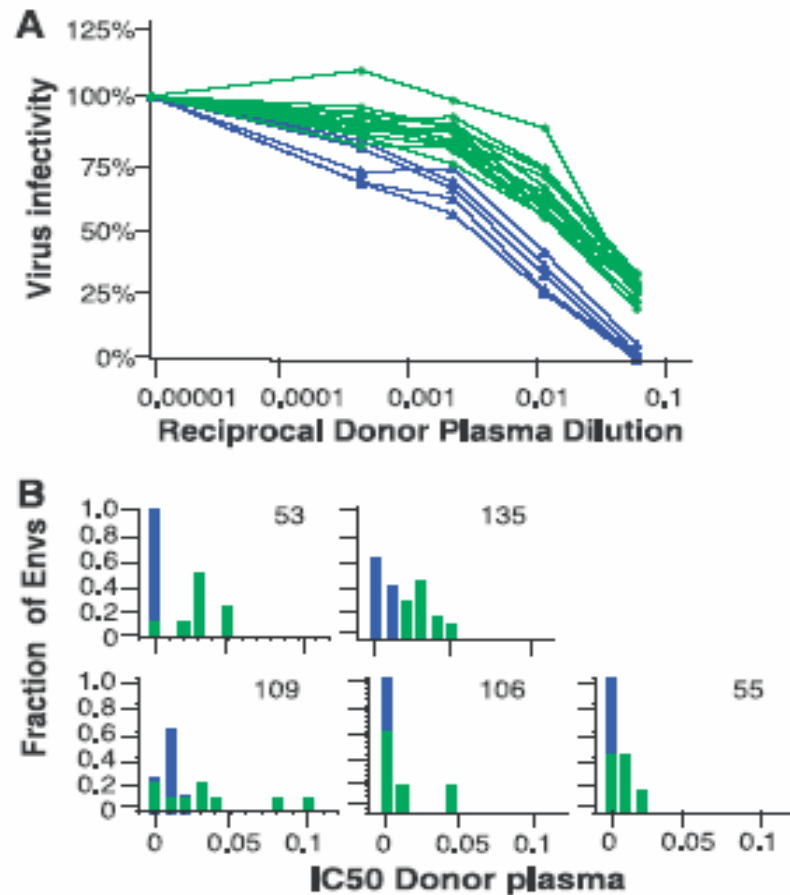


Source: Gray et al., *Lancet* 2001;257:1149



Properties of the Transmitted Virus

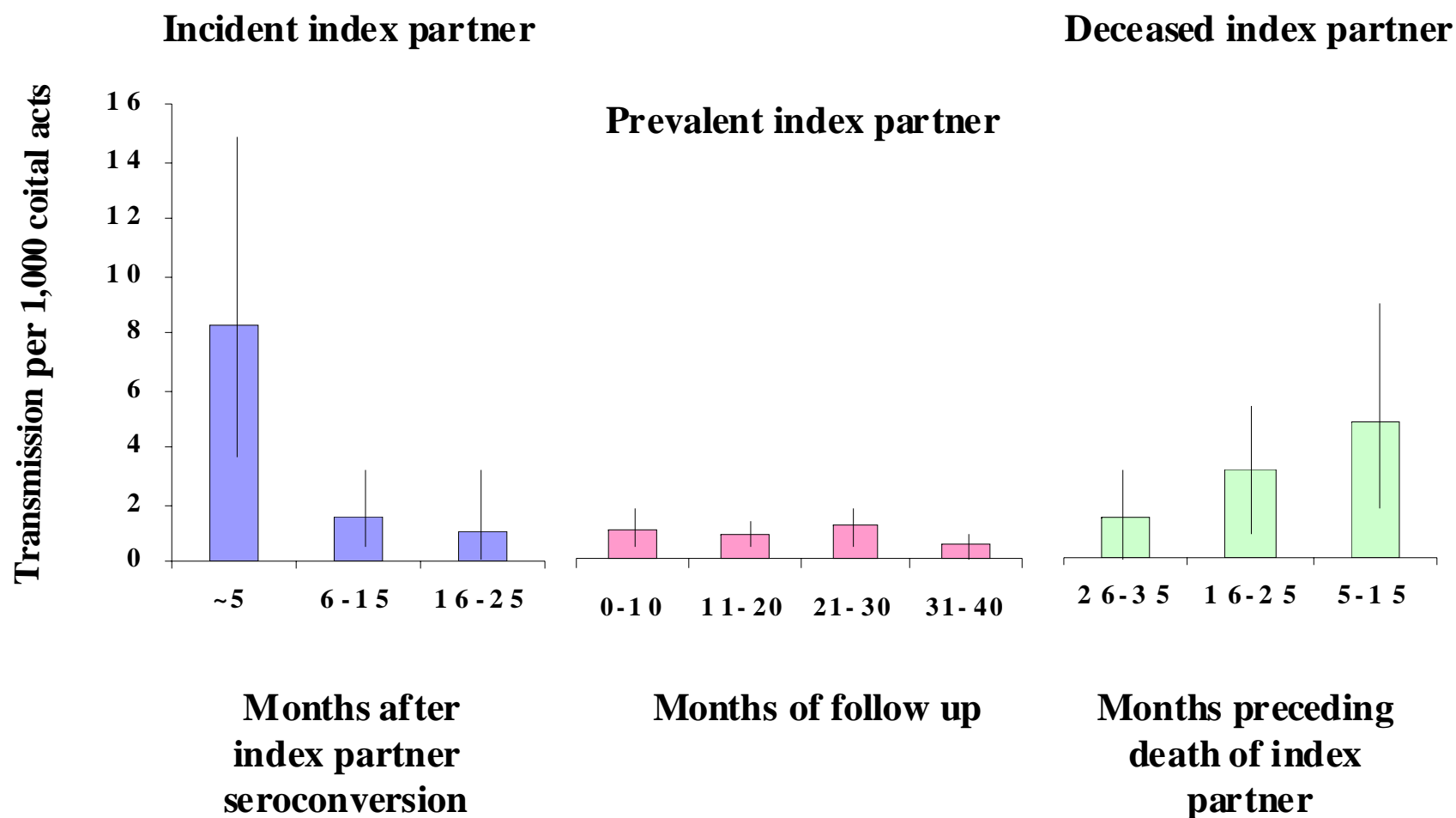
- The transmitted virus is neutralization sensitive and has shortened loops
- In a different study, Richman has shown transmitted virus (clade B) has low replicative capacity and hypersensitivity to a protease inhibitor

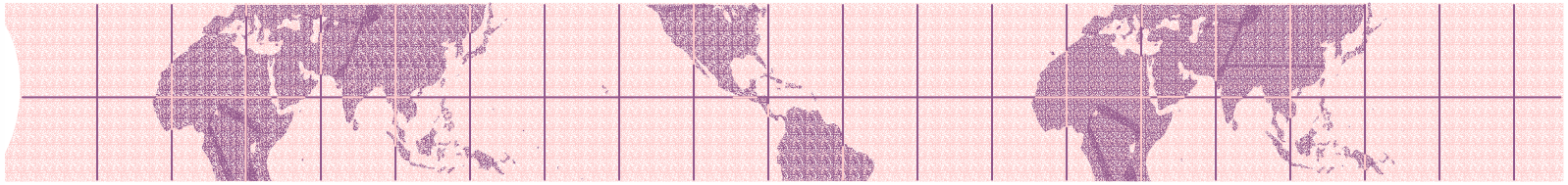


- Derdeyn et al. Science 303:2019-22 (2004)
- Leigh-Brown et al. J Virol 78:2242-6 (2004)



HIV Transmission is Driven by People in Early and Late Disease

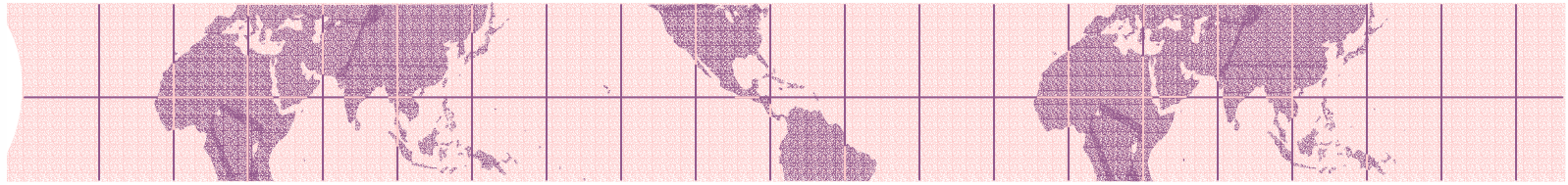




Summary and Conclusions:

- Risk of transmission is significantly increased early in infection
- Low during clinical latency
- Increases during late stage disease
- HIV that transmits is different than virus found in established infection
 - HIV adapts to each new host

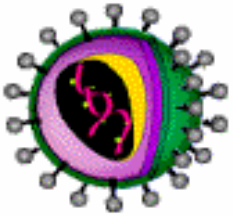
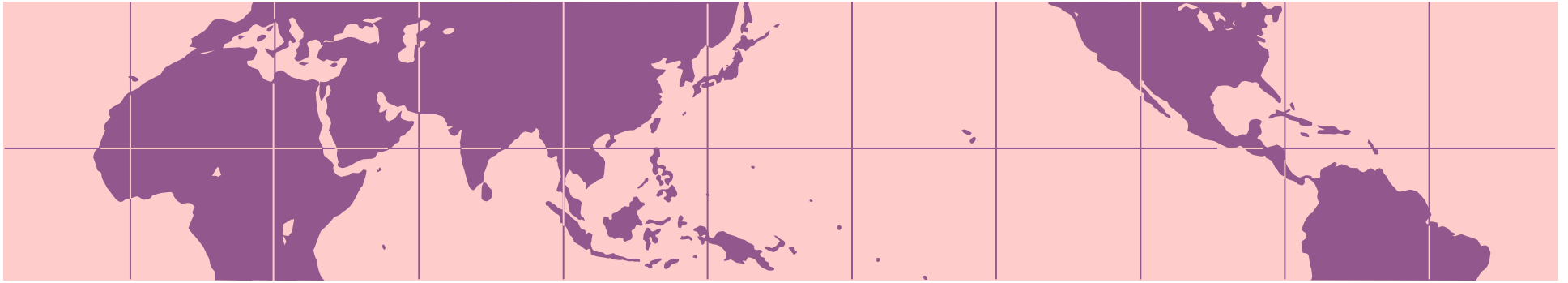




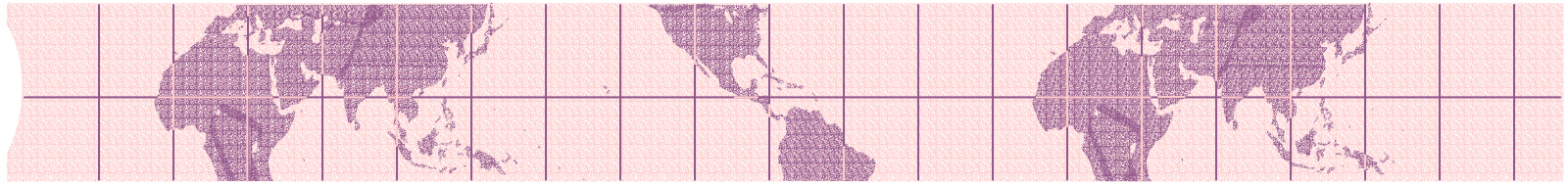
HIV Prevention –Translation of Knowledge of Mechanisms of Transmission (Biology *and* Behavior)

- **Vaccination**
- **Treatment with ART**
- **Microbicides**
- **STI Treatment**
- Voluntary counseling and testing
- Education and behavioral modification
- Drug abuse treatment
- Condoms, clean syringes





Questions?



Therapeutics Clinical Research: Objectives

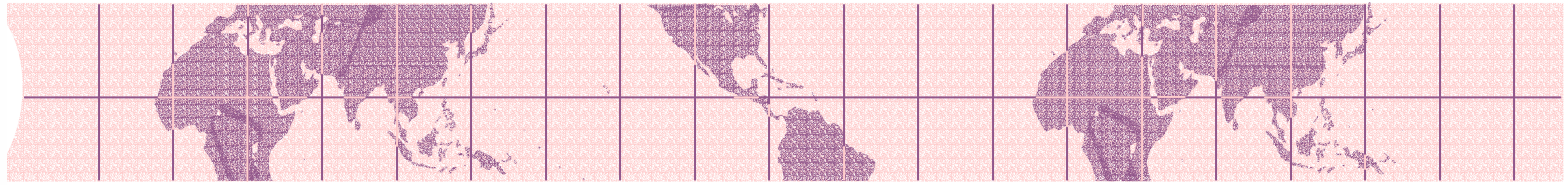
- To prevent HIV disease progression and deaths
 - Through the development of innovative strategies for antiretroviral treatment (ART) that provide *optimum* initial and subsequent ART regimens
 - Through effective use of new agents or novel classes of antiretroviral drugs, as they are developed



Therapeutics Clinical Research: Objectives

- **To identify, prevent and treat the complications of both HIV disease and antiretroviral therapies**
- **To prevent transmission of HIV infection and emergence of drug resistant virus in the community through therapeutic intervention**

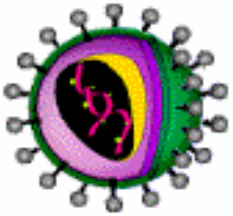
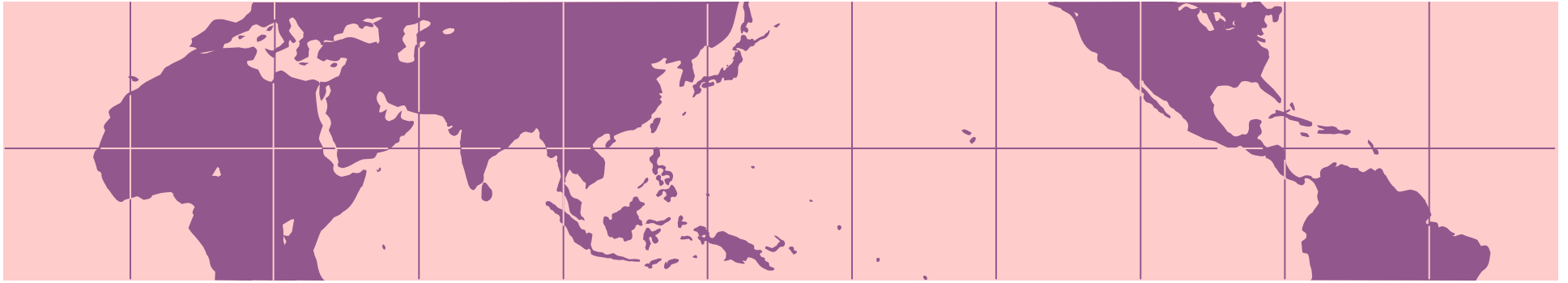




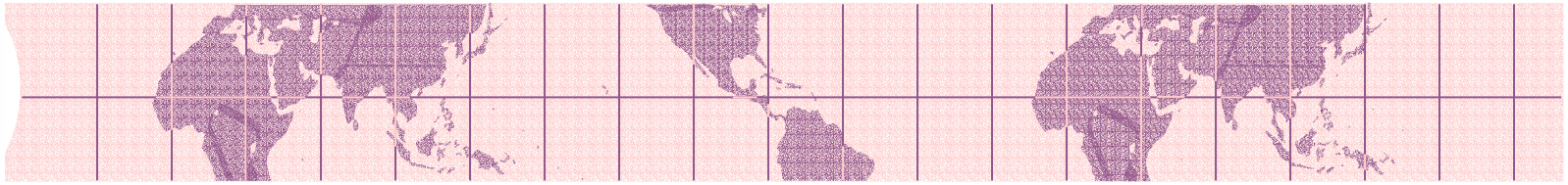
Therapeutics Clinical Research: Objectives

- **To “cure” HIV infection by developing strategies to eliminate reservoirs and eradicate infection – no detectable virus in absence of therapy**





**Where do we think
clinical therapeutics will
be in 2006 – 2013?**



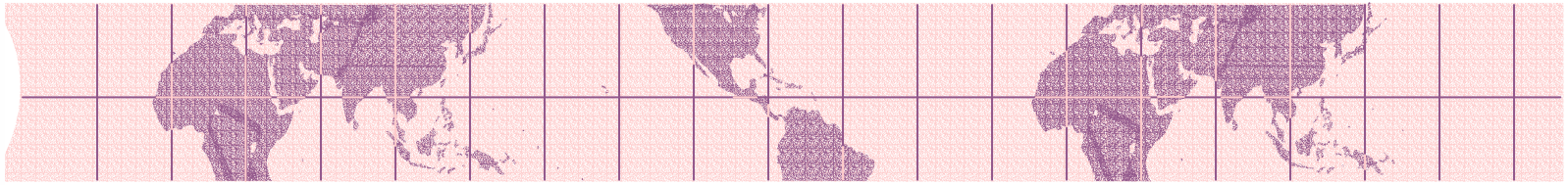
- **Drugs active against at least two new targets in HIV licensed for marketing or in late stage development**
 - Small molecule entry inhibitors – several targets
 - Integrase inhibitors
 - Maturation inhibitors
- **Fixed dose combinations becoming standard of care**





- **Progress toward integration of therapies to enhance immunity with antiviral agents**
 - IL2, IL7
 - Therapeutic vaccines
- **Agents for newer targets in clinical trials**
 - Vif:APOBEC 3G
 - TRIM5 alpha
 - Protein network of HIV budding
- **Rapid transition from preclinical to multicenter clinical trials to assess impact of new approaches**
 - Pathogenesis
 - Outcome of disease





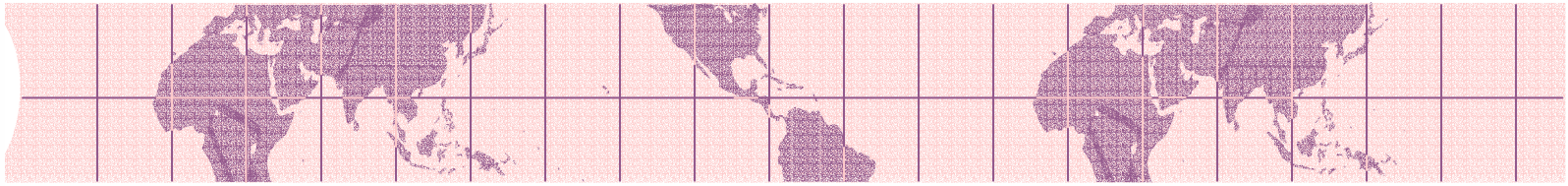
Therapeutics Clinical Research To Meet Medical Challenges



DHHS/NIH/NIAID/DAIDS

ARAC 5-24-04



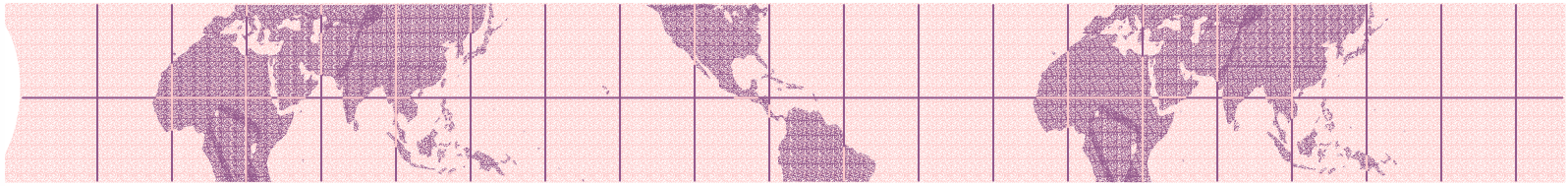


Therapeutics Clinical Research: Top Priority

➤ Translational Research/ Drug Development

- **Evaluate anti-HIV compounds aimed at novel mechanisms of action/new targets in studies that complement and expand research being done by industry**
- **Evaluate new therapies for patients with co-infections – especially Hepatitis C, TB, Malaria and Papillomavirus**



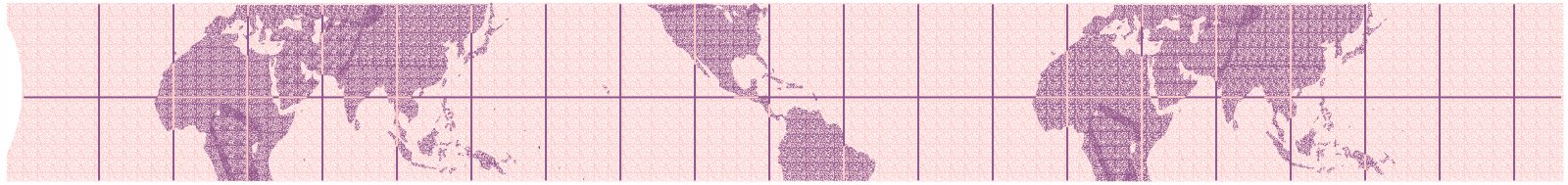


Therapeutics Clinical Research: Areas of Emphasis

➤ Translational Research/Drug Development

- In collaboration with industry, academia, and public/private partnerships

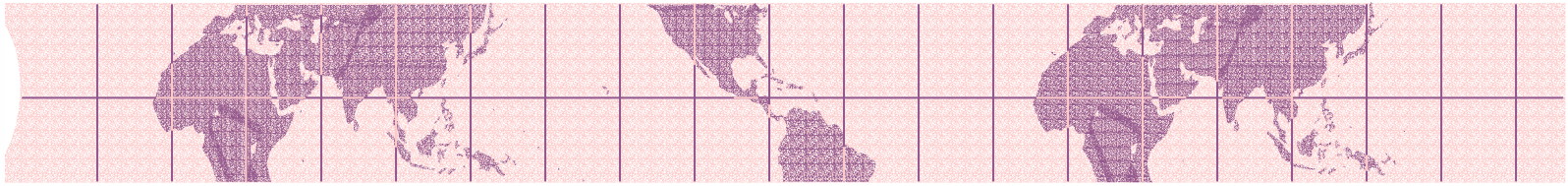




Therapeutics Clinical Research: Areas of Emphasis, Translational Research

- **Evaluate anti-HIV compounds aimed at novel mechanisms of action/new targets in studies that complement and expand research being done by industry**





AGENTS IN CLINICAL TRIALS

➤ Entry Inhibitors

- CCR5 blockers
 - Schering D
 - Pfizer UK 427,857
- GP120 blockers
 - PRO 542
 - BMS 378806
- CXCR4 blockers
 - AMD compound

➤ RT Inhibitors

- NRTI
 - Amdoxovir
- NNRTI
 - Capravirin
 - TMC-125
 - DPC 083

➤ Integrase Inhibitors

- Merck compounds
- GSK S-1360

➤ Protease inhibitors

- Atazanavir and Fosamprenavir recently approved
- Tipranavir
- Mozenavir
- TMC 114

➤ Cytokines

- Interleukin 2
- Interleukin 7

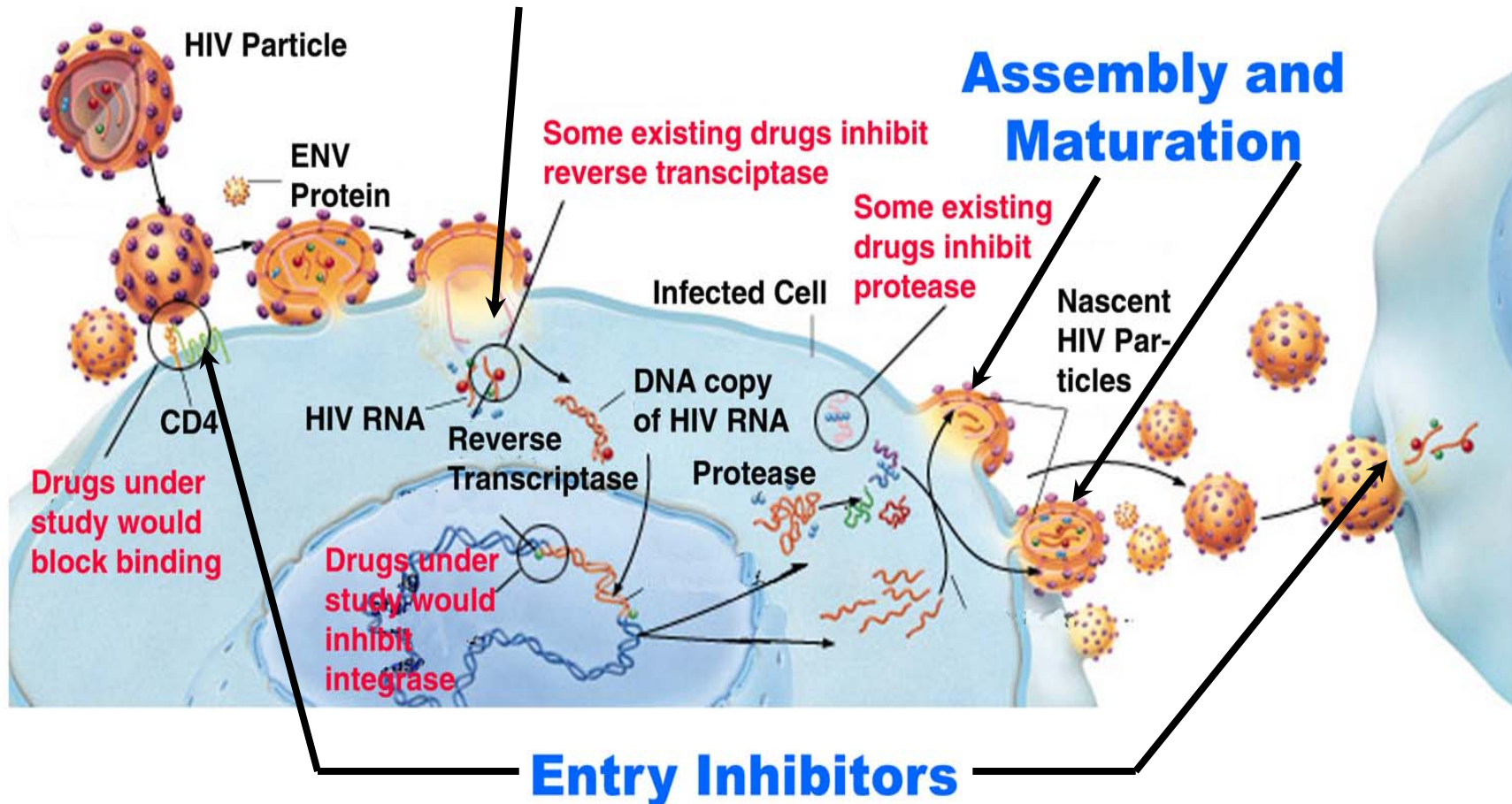
➤ Therapeutic vaccines

- MVA and adeno vectors



New Targets in HIV Life Cycle

APOBEC3G: VIF





**The Antiretroviral Enzyme
APOBEC3G is Degraded by
the Proteasome in
Response to HIV-1 Vif**

AM Sheehy, NC Gaddis & MH Malim

**HIV-1 Vif Protein Binds the
Editing Enzyme APOBEC3G
and Induces its Degradation**

M Marin, KM Rose, SL Kozak & D Kabat

*Possible
pharmacologic
strategy:
stabilizing
APOBEC3G in
HIV-1 infected
cells.*

Cell

Volume 114 Number 6

September 19, 2003

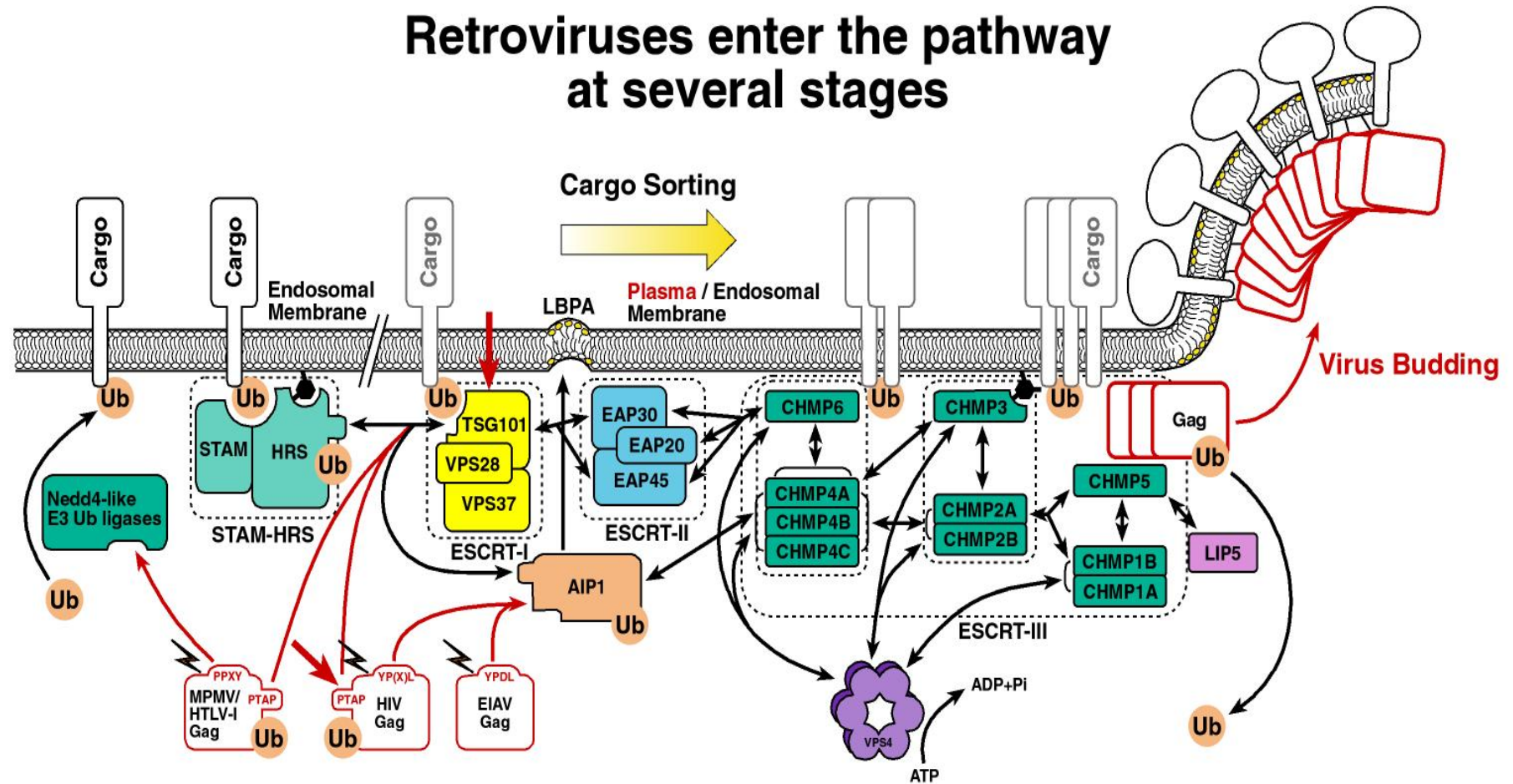
THE PROTEIN NETWORK OF HIV BUDDING

U.K. von Schwedler et al.

A network of 43 different protein-protein interactions participates in the release of HIV and probably many other viruses.

Virus Budding and MVB Vesicle Formation

Retroviruses enter the pathway at several stages



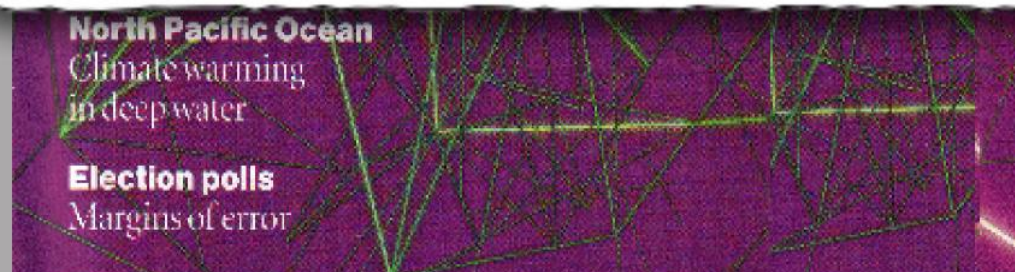
Courtesy of W. Sundquist (2004)

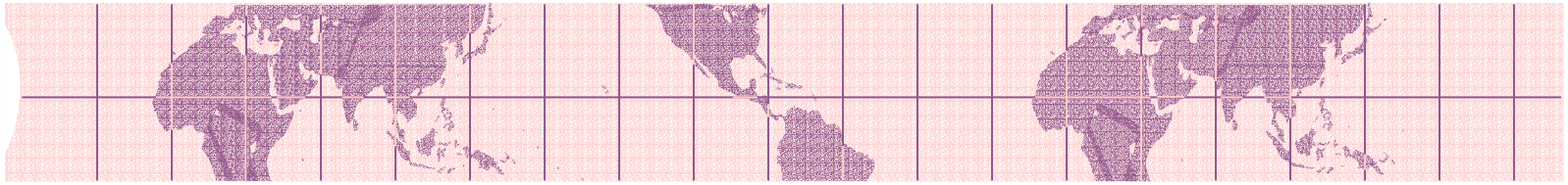


The Cytoplasmic Body Component TRIM5 Restricts HIV-1 Infection in Old World Monkeys

**M Stremlau, CM Owens, MJ Perron, M
Kiessling, P Autissier & Sodroski J.**

**"This is the first
glimpse of a form
of intracellular
immunity made
up of natural
factors that
specifically and
potently block
retroviruses
such as HIV-1."**





Therapeutics Clinical Research: Areas of Emphasis, Translational Research-2

- **Therapies for patients with co-infections, especially Hepatitis C, TB, Malaria and Papillomavirus**
- **Therapies to manage co-morbidities**

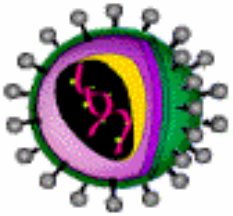
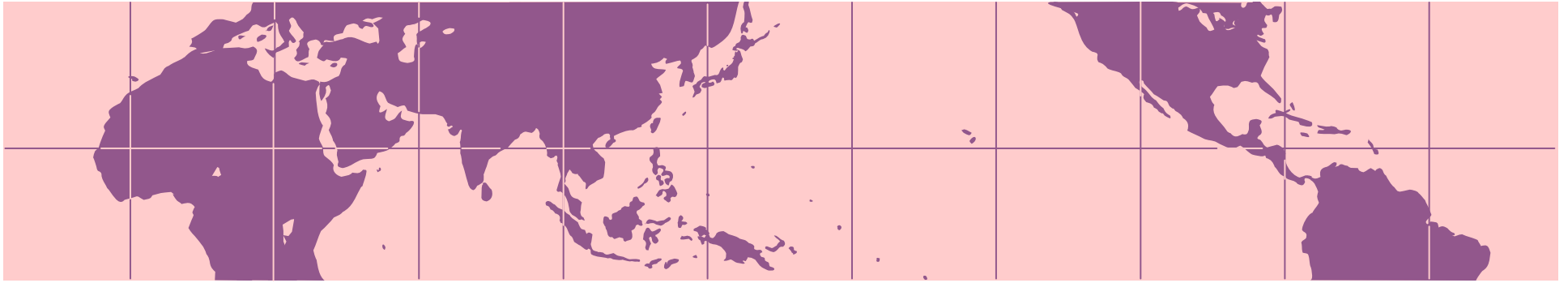




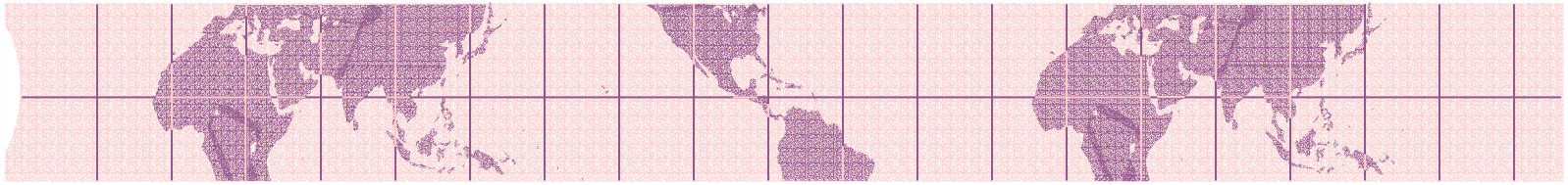
Therapeutics Clinical Research: Areas of Emphasis

- Test new hypotheses generated by pathogenesis studies
- Conduct pharmacokinetic studies in children and adolescents to enable licensure and optimize use
- Integrate immune-based therapies in treatment regimens, emphasizing mechanisms of antiviral effect and immune reconstitution



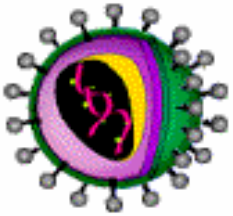
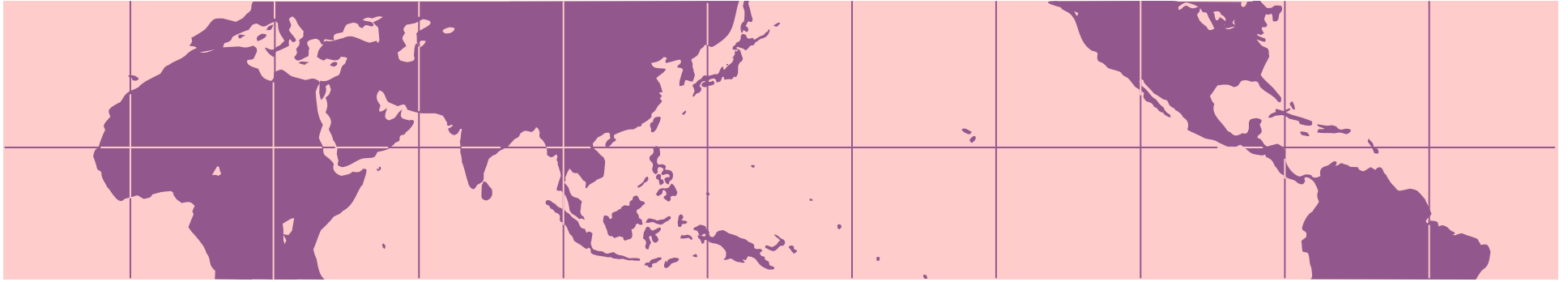


Questions?



Vaccine Clinical Research and Development: Objectives

- **Identify a vaccine that is safe and effective (at least partially)**
 - **Benefit the individual**, e.g. prevent infection or progression
 - **Benefit public health benefit**, e.g. prevent transmission
- **Decipher correlate(s) of immune protection**
- **Apply worldwide**, e.g. all clades, exposures, HLA, etc.



**Where do we hope the
vaccine field will be in
2006 - 2013?**

SPECIAL NEWS FOCUS ON MALARIA

20 October 2000

Science

Vol. 290 No. 5491

Control of Viremia and Prevention of Clinical AIDS in Rhesus Monkeys by Cytokine-Augmented DNA Vaccination

Dan H. Barouch, et al.

Science

6 April 2001

Control of a Mucosal Challenge and Prevention of AIDS by a Multiprotein DNA/MVA Vaccine

Rama Rao Amara, et al.

7 September 2001

Cell

An Effective AIDS Vaccine Based on Live Attenuated Vesicular Stomatitis Virus Recombinants

Nina F. Rose, et al.

17 January 2002

International weekly journal of science

nature

Replication-Incompetent Adenoviral Vaccine Vector Elicits Effective Anti-Immunodeficiency-Virus Immunity

John W. Shriver, et al.

THE WALL STREET JOURNAL

February 27, 2002

Merck Shows AIDS Vaccine's Action In Humans as Scientists Hail Studies

By MARK SCHOOF
Staff Reporter of THE WALL STREET JOURNAL



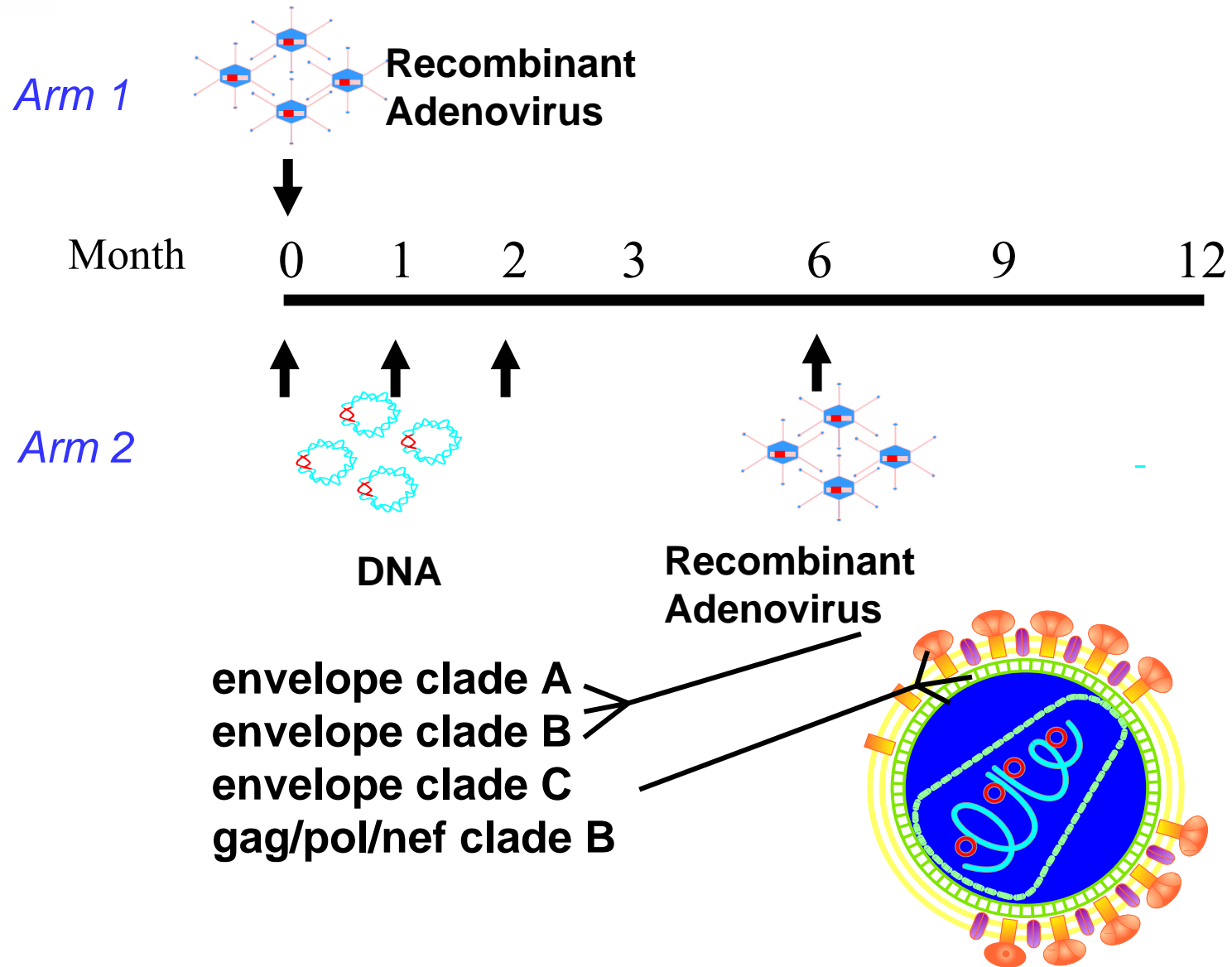
National Institute of Allergy and Infectious Diseases • National Institutes of Health

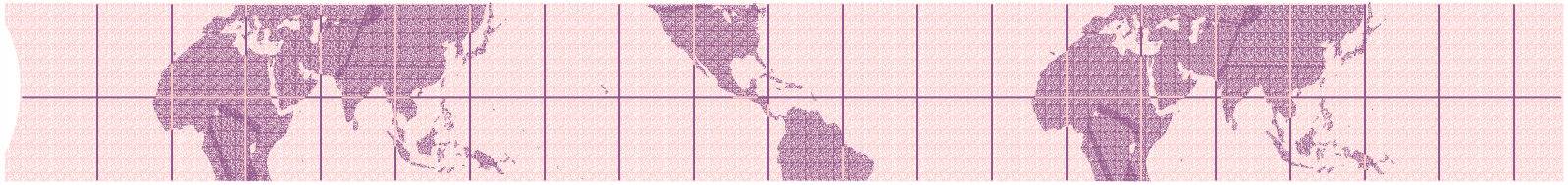
FOR RELEASE
December 20, 2001

NIAID and Merck to Collaborate on HIV Vaccine Development



NIAID VRC Candidate Vaccines





Ongoing + potential NIAID supported efficacy trials

- | | |
|----------------------------------|--------------|
| ➤ Canarypox + gp120 ^a | 2003 – 2009 |
| ➤ Adenovirus ^b | 2004 – 2009+ |
| ➤ DNA + Adenovirus ^c | 2006 – 2010+ |

^a USMHRP, Royal Thai government; ^b Merck; ^c VRC

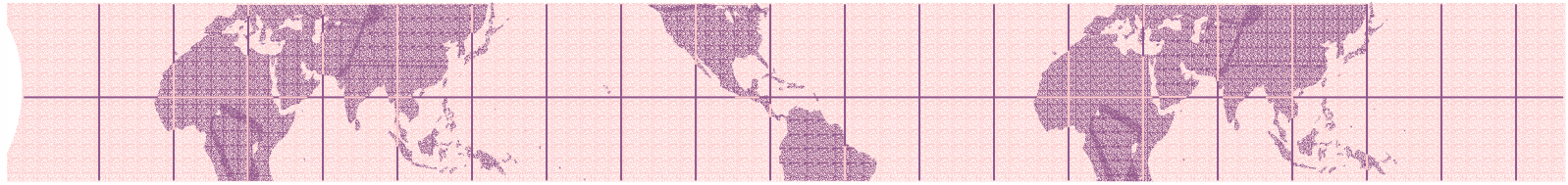




Candidates in Phase I/II Trials

- **DNA vectors**
 - DNA-polyepitope-gag (C) (IAVI/Oxford/Kenya/Uganda)
 - **DNA-gag-pol,nef; env (A,B,C) (NIAID VRC)**
 - **DNA-multigene (B) (Emory/GeoVax/CDC/NIAID)**
 - DNA-multigene (C) (EuroVacc)
 - **DNA-multi-epitope (Epimmune/NIAID)**
- **Viral vectors and combinations**
 - Adeno-gag; pol; nef (B) (Merck) +/- ALVAC boost (AvP)
 - **Adeno-env,gag,pol (A,B,C) (NIAID VRC)**
 - **VEE-gag (C) (AlphaVax/NIAID/IAVI)**
 - Adeno-associated Virus (C) (Targeted Genetics/IAVI)
 - NYVAC (C) (EuroVacc)
- **DNA Combinations**
 - DNA + MVA, multi-epitope + gag (A) (IAVI)
 - **DNA + FP multi-gene (B) (UNSW/NIAID)**
 - **DNA-env + Env (B) (Chiron/NIAID)**
- **Other**
 - **Tat-nef +/- gp120 in AS02-A (B) (SKB)**
 - Tat (ISS)
 - **ALVAC + Lipopeptides (B) (ANRS, AvP, NIAID)**

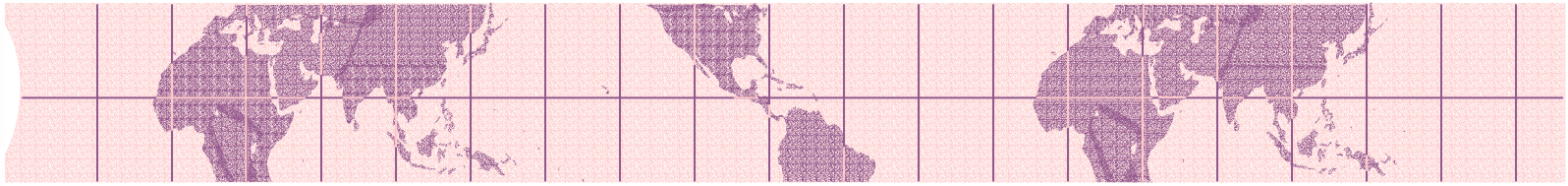




Approaches to New Envelope Immunogens

- **Stablize and/or expose conserved conformational epitopes**
 - Disulfide bridges
 - Other amino acid changes
 - Remove variable loop(s)
 - Remove glycosylation site(s)
- **Mimic entry intermediate**
 - CD4 or CD4-mimetic bound
- **Construct native trimeric form**

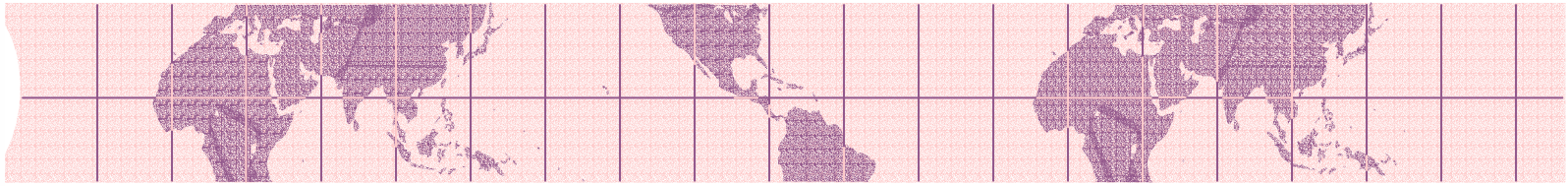




- Ongoing + potential NIAID supported efficacy trials underway
 - Canarypox + gp120^a 2003 – 2009
 - Adenovirus^b 2004 – 2009+
 - DNA + Adenovirus^c 2006 – 2010+
- **Narrowed pipeline of candidates in clinical trial**
- **Better envelope immunogens ?**

^a USMHRP, Royal Thai government; ^b Merck; ^c VRC





Vaccine Clinical Research

➤ Phase 1 and 2 trials

- **Identify and compare candidates; down select and advance**
 - Broadly reactive Ab; improved vectors
- **Test and compare combinations and adjuvants**
 - Address anti-vector immunity
 - Optimize immunogenicity and safety
- Evaluate host factors that may impact outcomes
 - gender, HLA, etc
- Pursue innovative approaches
 - mucosal immunization, enhanced innate immunity, etc

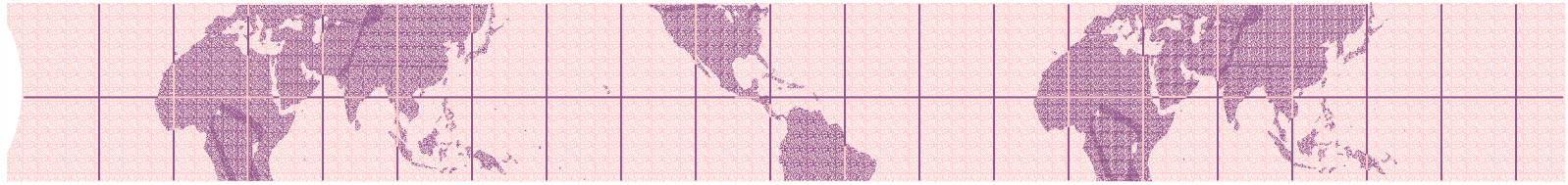




Vaccine Clinical Research

- **Evaluate candidates in phase 2b/3 in highest risk populations**
 - **Include women, and minorities**
 - **Identify immunologic, virologic correlates of protection**
 - **Link with animal model studies**
- **Develop cohorts and collect epi info to prepare**
 - **Consider community based trials as warranted**
- **Decipher relevance of genetic subtypes**
- **Other clinical research; role genomics, HLA, etc**



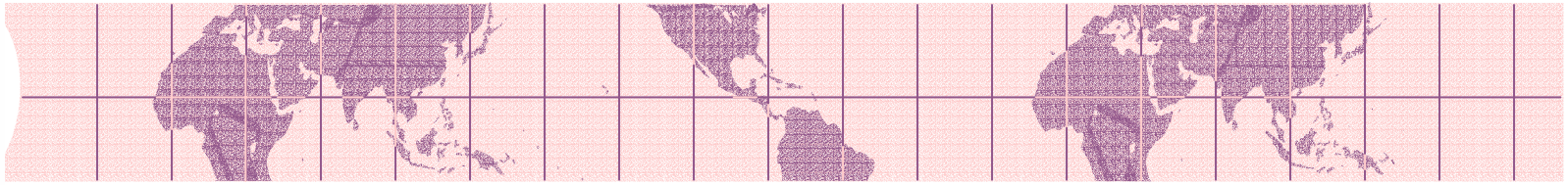


Vaccine Clinical Research

➤ Evaluate immune responses

- **Develop methods to optimize signal**
 - collection, processing, freezing, shipping
 - peptide pools to make relevant comparisons
- **Validate assays to be used in pivotal trials**
- **Implement QA/QC programs**
- **Develop new assays to measure full breadth of induced immune responses**
- **Make specimens available to others**

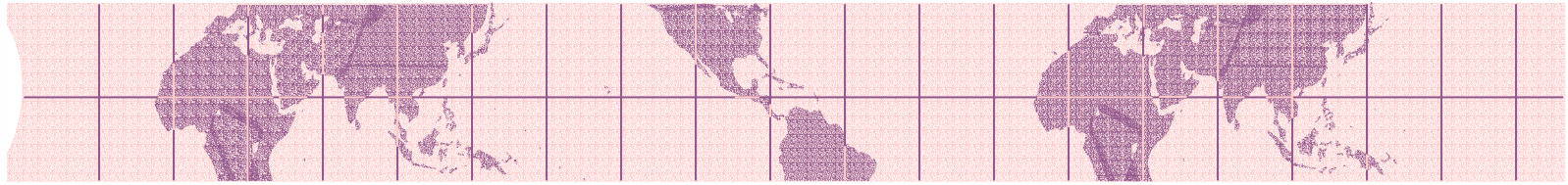




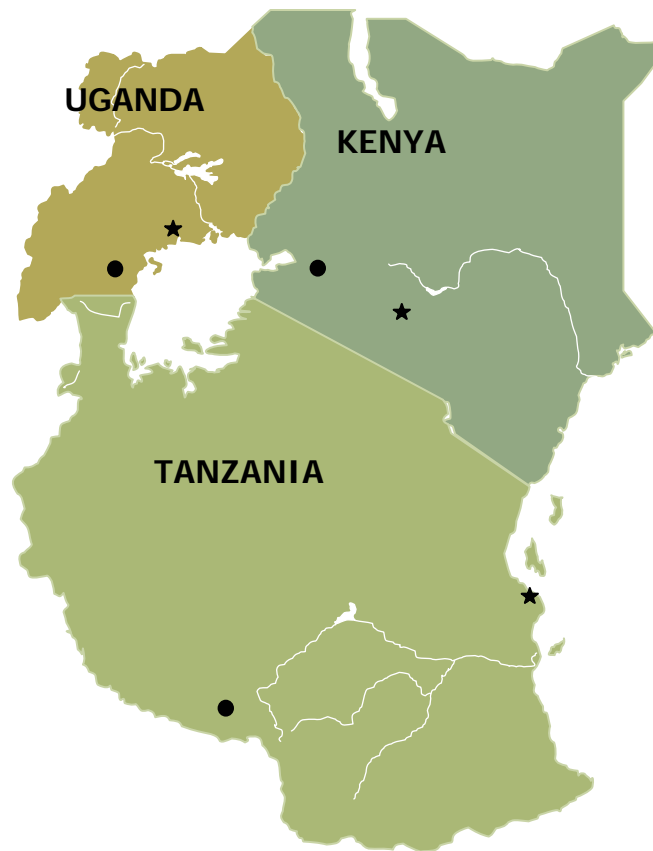
Vaccine Clinical Research

- **Standardize, optimize trial designs**
 - **Accelerate pace of evaluation**
 - **Ensure rapid licensure in special populations, all at-risk groups, adolescents (NICHD)**
- **Contribute to discussions to facilitate US and international licensure**





USMHRP Vaccine Cohort Development and Testing Sites East Africa



Partnership for AIDS Vaccine Evaluation (PAVE)

- **A partnership, facilitated by NIAID, between the 3 U.S. governmental agencies involved in clinical HIV/AIDS vaccine research.**
- **Purpose: Serve as a forum and clearing house to achieve better harmony and increased operational and cost efficiency.**
- **Philosophy: The contribution and unique identity of each cooperating entity will be maintained and recognized.**
- **Initial focus: Preparing for phase III trials.**
- **Future: Additional activities as development progresses.**

The image shows the top portion of a Science journal cover. The word "Science" is printed in a large, white, serif font against a dark blue background. Above it, the date "27 June 2003" is printed in a smaller white font. Below the title, the volume and issue information "Vol. 300 No. 5628" and the page range and price "Pages 1989-2124 \$10" are printed in a small white font. The entire cover is set against a larger blue background.

Science

27 June 2003

Vol. 300 No. 5628
Pages 1989-2124 \$10

The Need for a Global HIV Vaccine Enterprise

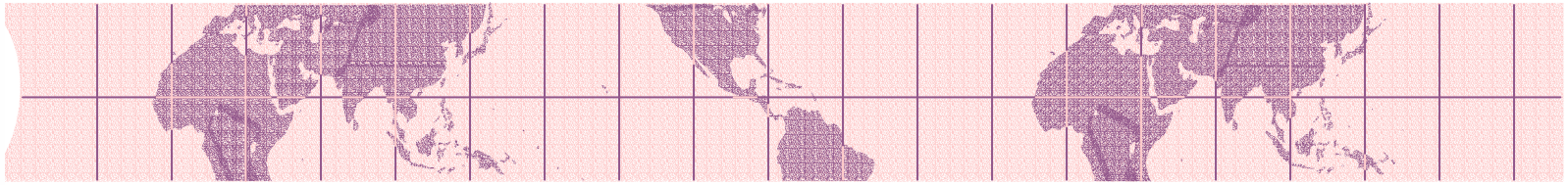
**R.D. Klausner, A.S. Fauci, L. Corey, G.J. Nabel, H. Gayle,
S. Berkley, B.F. Haynes, D. Baltimore, C. Collins, R.G. Douglas,
J. Esparza, D.P. Francis, N.K. Ganguly, J.L. Gerberding,
M.I. Johnston, M.D. Kazatchkine, A.J. McMichael, M.W. Makgoba,
G. Pantaleo, P. Piot, Y. Shao, E. Tramont, H. Varmus,
J.N. Wasserheit**

Meeting on "A Global Vaccine Enterprise"

Airlie, Virginia

August 19, 2003

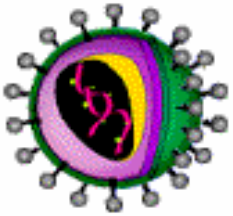
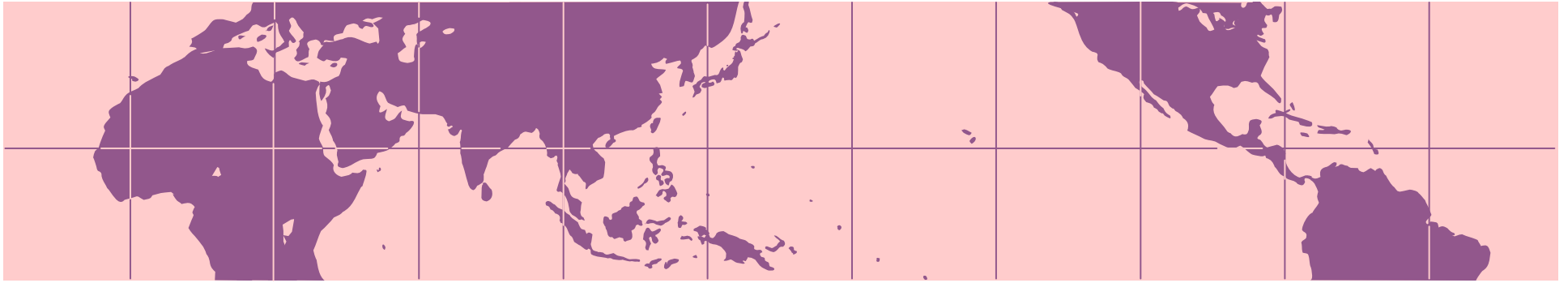
"The vision of the group is to help accelerate the development of an HIV vaccine at a global level by the establishment of an alliance of multiple independent entities united by the moral commitment to participate in the execution of a global strategic plan."



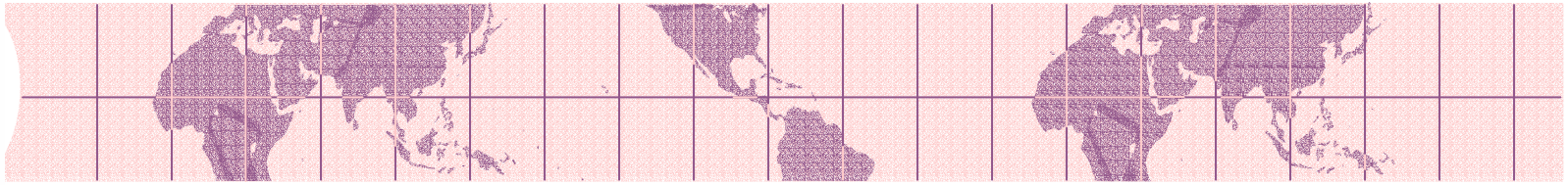
Vaccine Clinical Research

- **Collaborate with others on R&D**
 - **Lab assays for cross-system comparisons – PAVE, Enterprise**
 - **Trials with industry and other networks as needed (DoD, EU, SAAVI, others)**
 - **Other ICs and other networks**
 - Vaccines for prevention of MTCT
 - Therapeutic vaccines
 - Cancer vaccines (NCI)





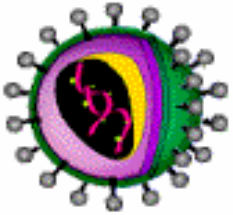
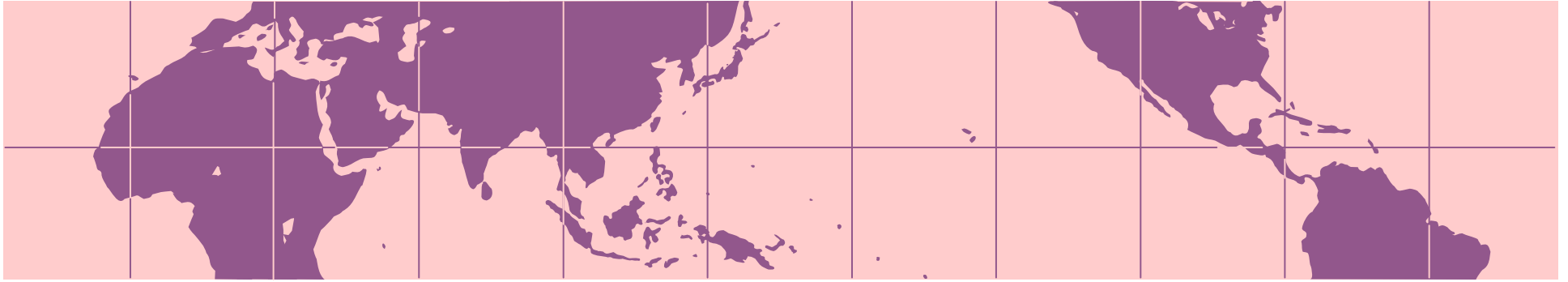
Questions?



Microbicide Clinical Research and Development: Objectives

- **Identify a microbicide that is very safe and effective (at least partially)**
- **Determine correlates of short and long term safety**
- **Evaluate and optimize acceptability and adherence**





**Where do we think the
microbicide field will be in
2006 – 2013?**

Topical Microbicides

*Preventing Sexually
Transmitted Diseases*

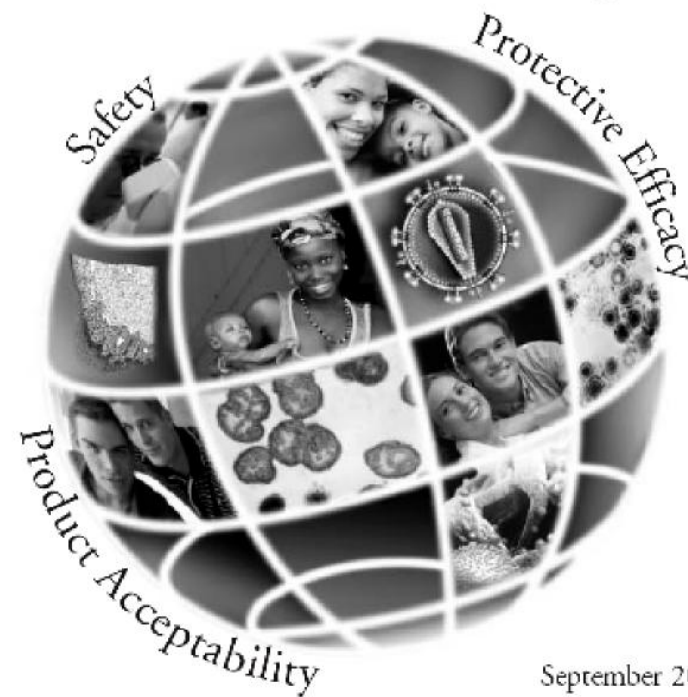


U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases

NIAID

Topical Microbicide

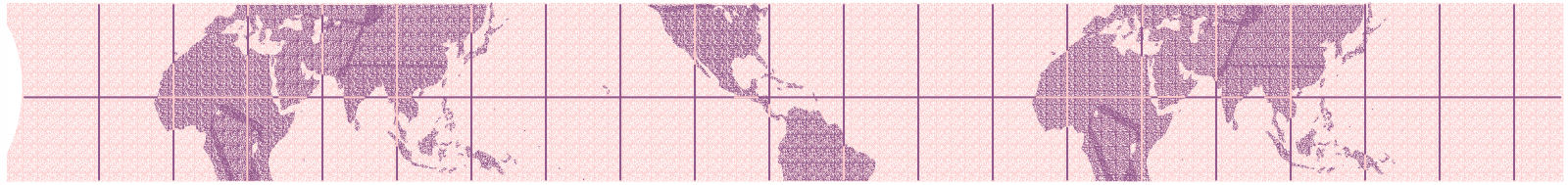
Strategic Plan



September 2003

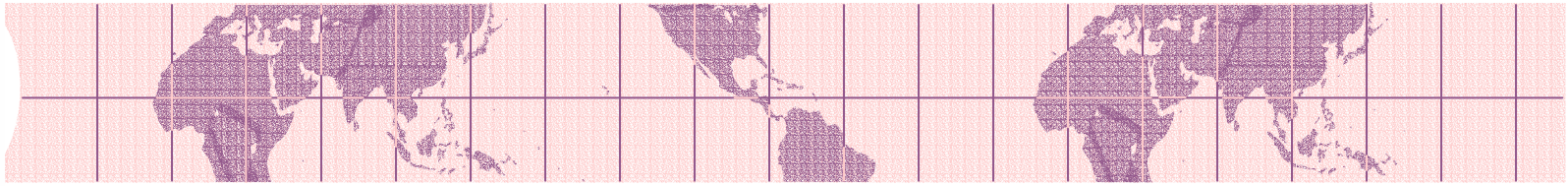


U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases



- **NIAID efficacy trial planned**
 - Pro2000(5), BufferGel 2004 – 2008
- **Other product(s) poised for efficacy trial**
 - PMPA gel? Others?
- **More interesting preclinical pipeline**
 - HIV-specific agents, including R5 inhibitors
 - Agents/combinations that attack multiple steps in replication cycle





- **CDC = Centers for Disease Control and Prevention**
- **DMID = NIAID Division of Microbiology and Infectious Diseases**
- **NCI = National Cancer Institute**
- **NHLBI = National Heart, Lung and Blood Institute**
- **NIA = National Institute on Aging**
- **NICHD = National Institute of Child Health and Human Development**
- **NIDA = National Institute on Drug Abuse**
- **NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases**
- **NIMH = National Institute of Mental Health**
- **NINDS = National Institute of Neurological Disorders and Stroke**
- **USAID = United States Agency for International Development**



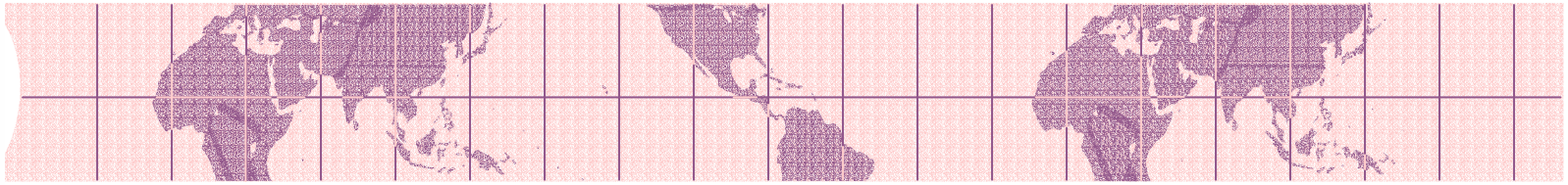


Microbicide Clinical Research

(DMID, NICHD)

- **Conduct all phases of clinical research**
 - **Focus on products with appropriate safety profile (daily use), multiple mechanisms of attack; combinations**
 - X4/R5 HIV; resistance; other STIs; high vs low frequency users; adolescents; (conception/pregnancy)
 - **Phase 1-2**
 - **Evaluate best in phase 2b/3 trials**



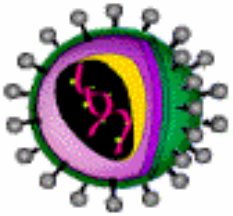
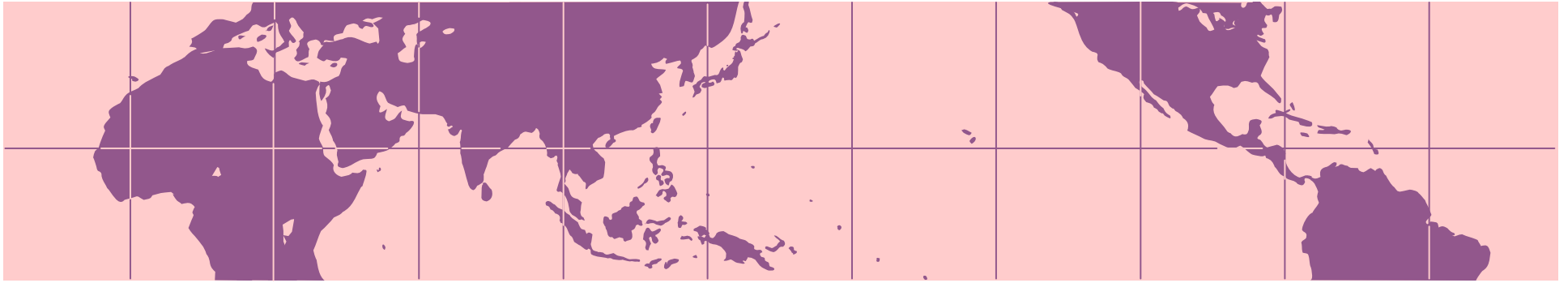


Microbicide Clinical Research

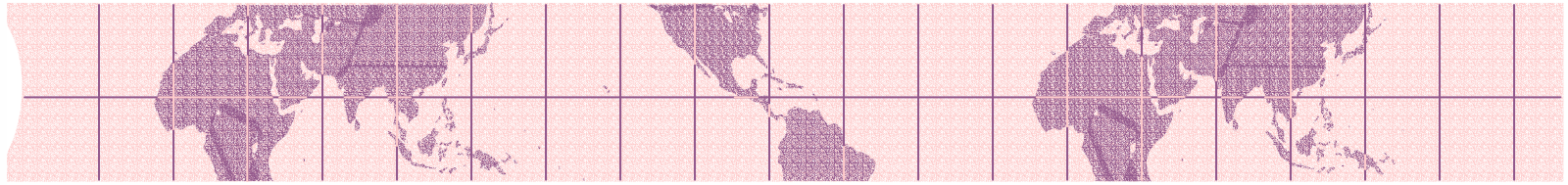
(NICHHD, CDC, USAID)

- **Evaluate user and partner acceptability and adherence (NIMH)**
 - short and long term
 - behavioral and cultural factors
- **Explore correlates of safety (and efficacy)**
- **Conduct research on rectal safety**
- **Evaluate delivery approaches; single formulation; intercourse dissociated**





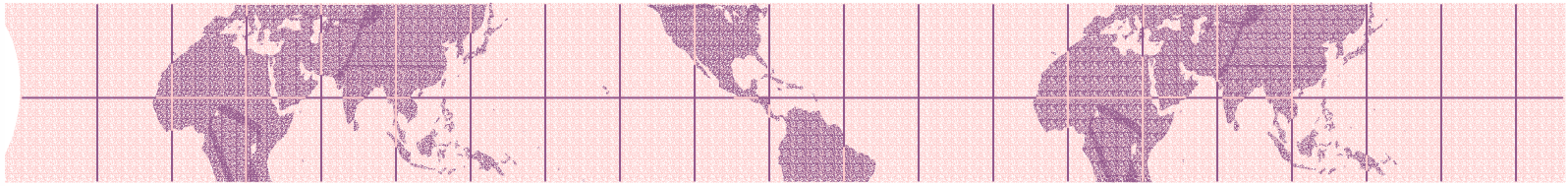
Questions?



Therapeutics Clinical Research: Areas of Emphasis-priority #2

- **Optimization of Clinical Management**
 - **Domestically and internationally**

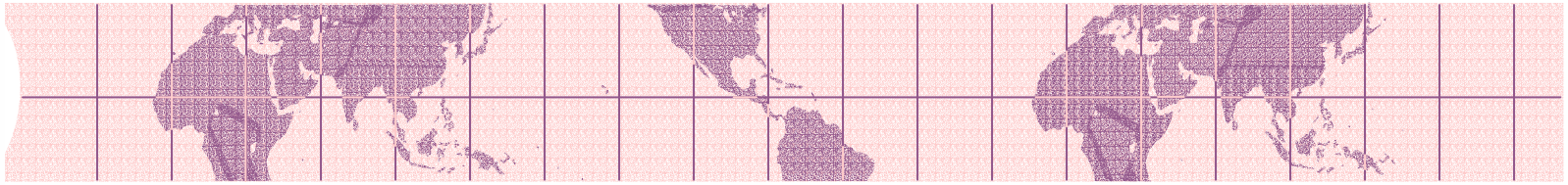




Areas of Emphasis: Therapeutics Research Optimization of Clinical Management

- **Study effectiveness of new regimens, with priority for those that incorporate agents with novel mechanisms of action or new treatment combination strategies**
- **Evaluate therapies for co-infections**
 - Prophylaxis
 - Acute treatment
 - Interaction with antiretroviral agents.
- **Optimize therapies on the basis of safety, adherence, resistance, durability of response and prevention of transmission**





Optimization of Clinical Management :

With NCI, NIDDK, NHBLI, NIMH, NINDS, NIA

- Integrate studies of malignancies, particularly KS and those associated with viral hepatitis, papillomavirus, and EBV into research agenda
- Facilitate treatment and evaluation of metabolic abnormalities, co-morbidities and complications of ARV therapy and/or progressive HIV infection – with other ICs with special expertise

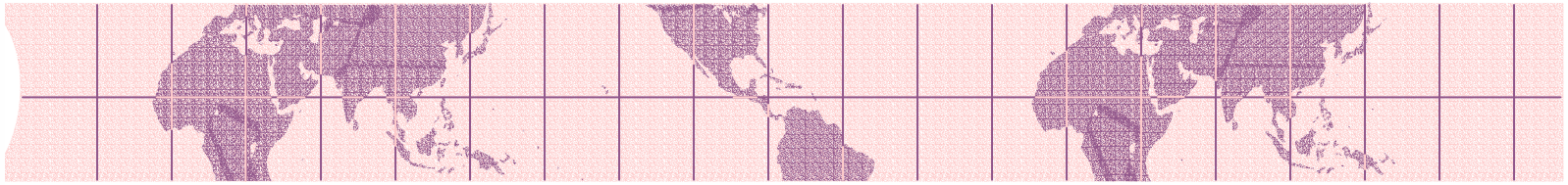




Overarching Principles for All Studies

- Identify underserved or disenfranchised populations (e.g. women, minorities, adolescents, young children)
- Specify barriers to participation in clinical research for these and other special populations
- Develop strategies to address the problems identified above

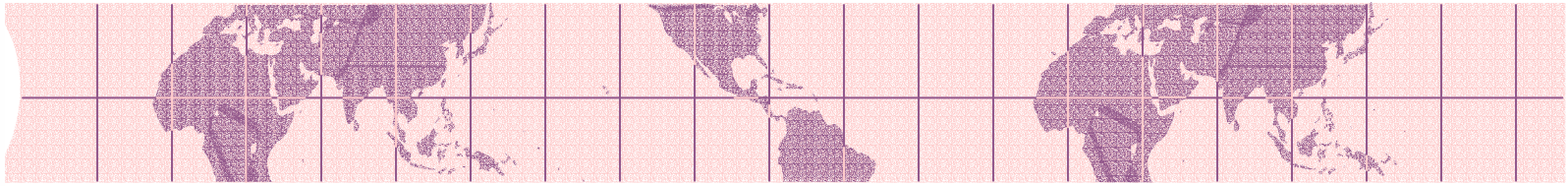




Overarching Principles for All Studies

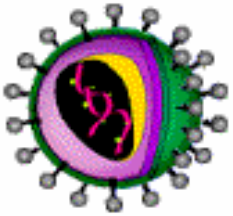
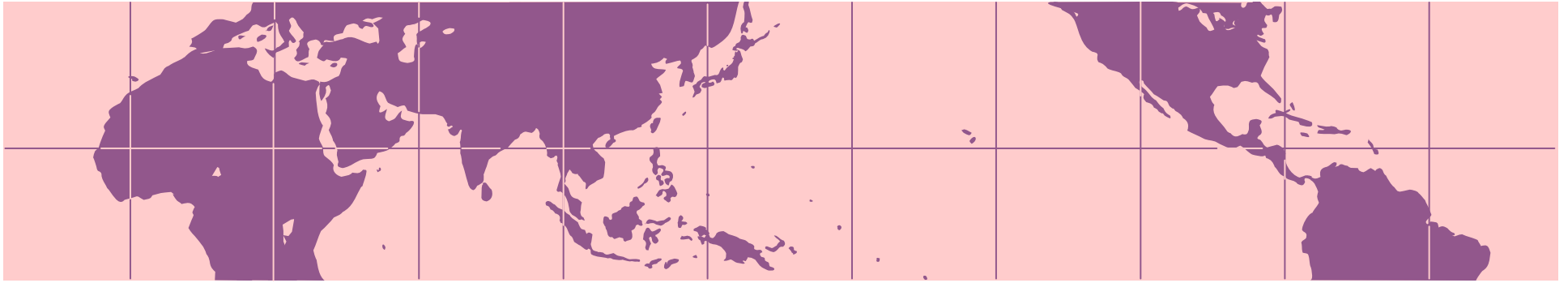
- **Incorporate studies of acutely infected individuals in all aspects of therapeutics research – particular focus on role of early interventions in modifying viral set point, long term outcome and transmission rates**
- **Pharmacogenomics – Investigate the role of individual and population genetic differences in responses to therapy, incidence of complications and co-infections, and course of disease (co-morbidities)**



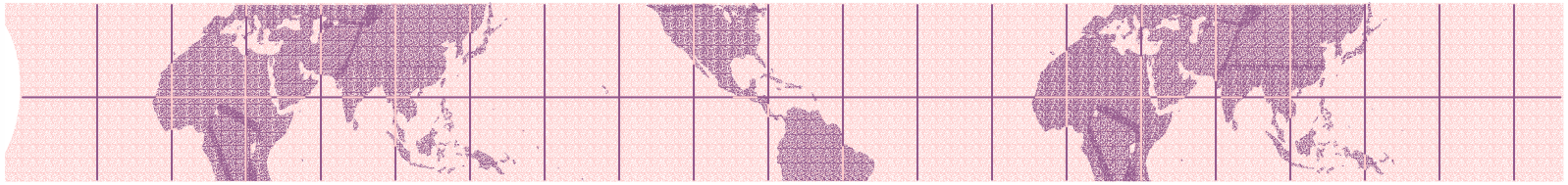


Therapeutics Clinical Research: Top Priorities

- **Optimization of Clinical Management**
 - **Study Effectiveness of new regimens, with priority for those that incorporate agents with novel mechanisms of action or new treatment combination strategies**
 - **Evaluate therapies for co-infections**
 - **Optimize therapies on the basis of safety, adherence, resistance, durability of response and prevention of transmission**



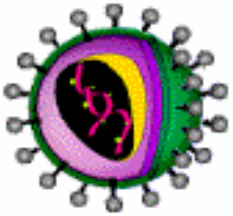
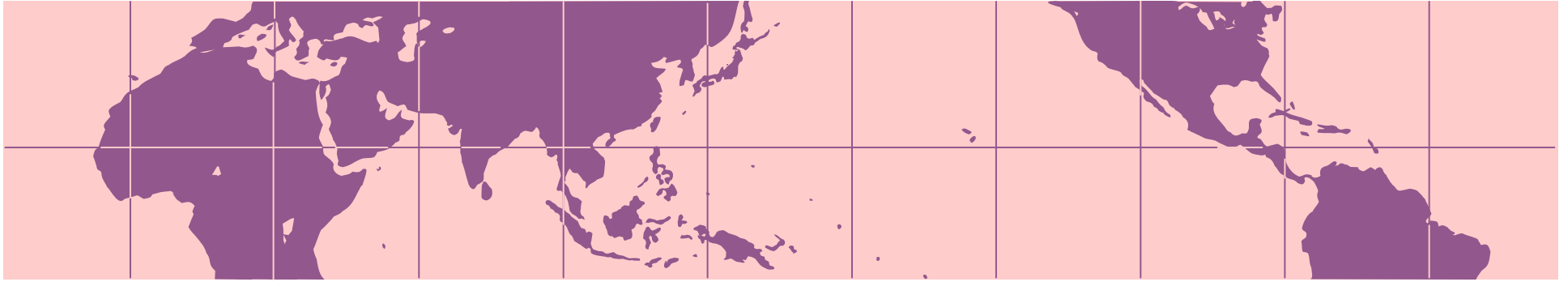
Questions?



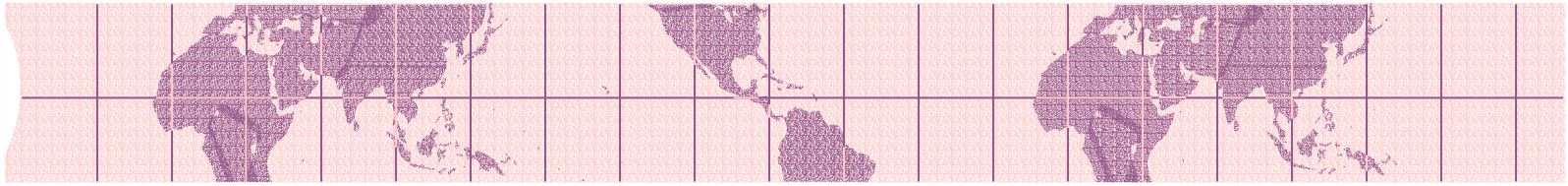
Prevention Clinical Research: Objectives

- **Identify more practical, safe and effective approaches to halt the spread of HIV**
 - **Especially in populations where HIV is spreading most rapidly**
- **Evaluate worldwide suitability and sustainability of those approaches**

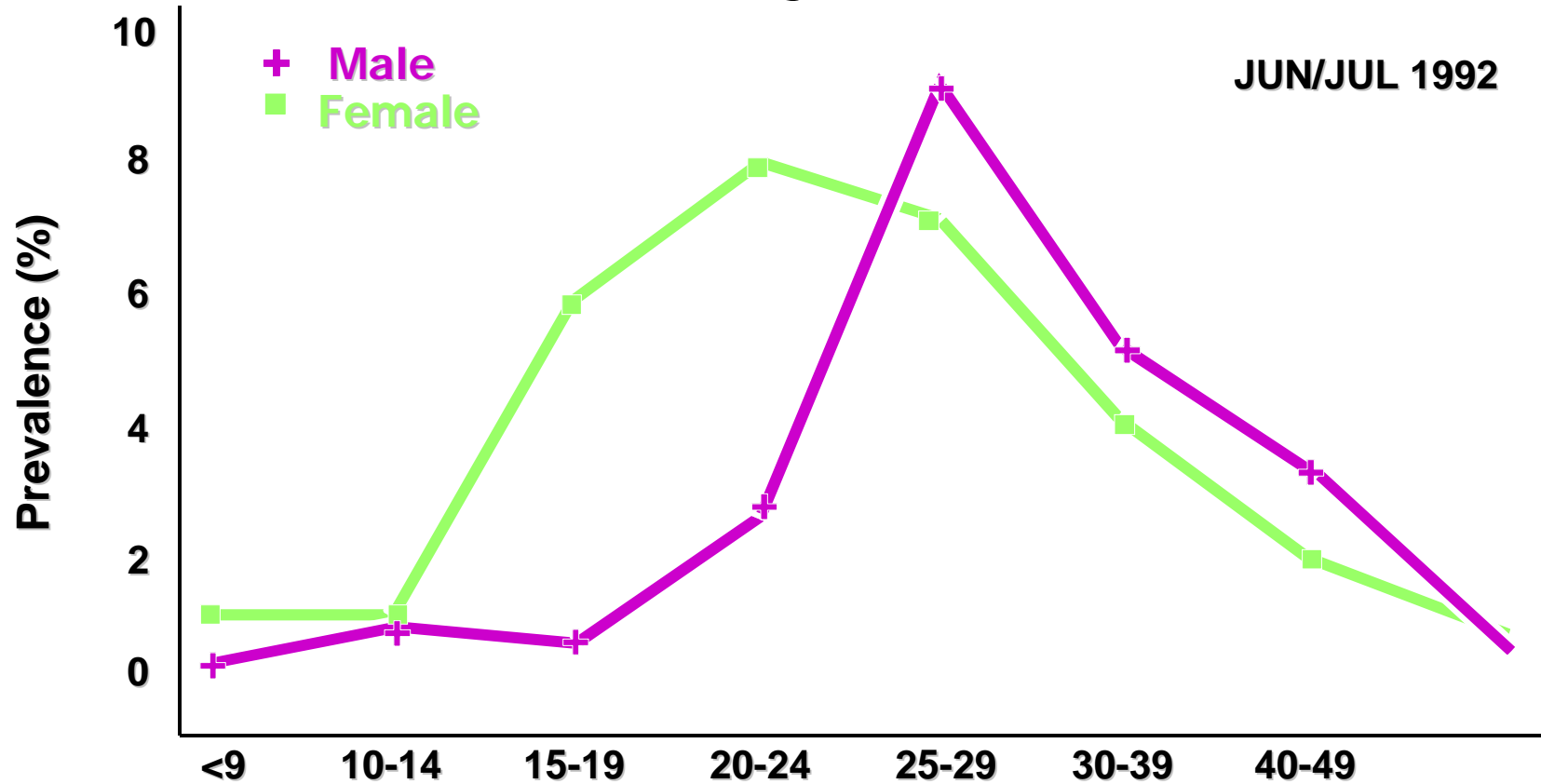




**Where do we think the
prevention research field
will be in 2006 – 2013?**

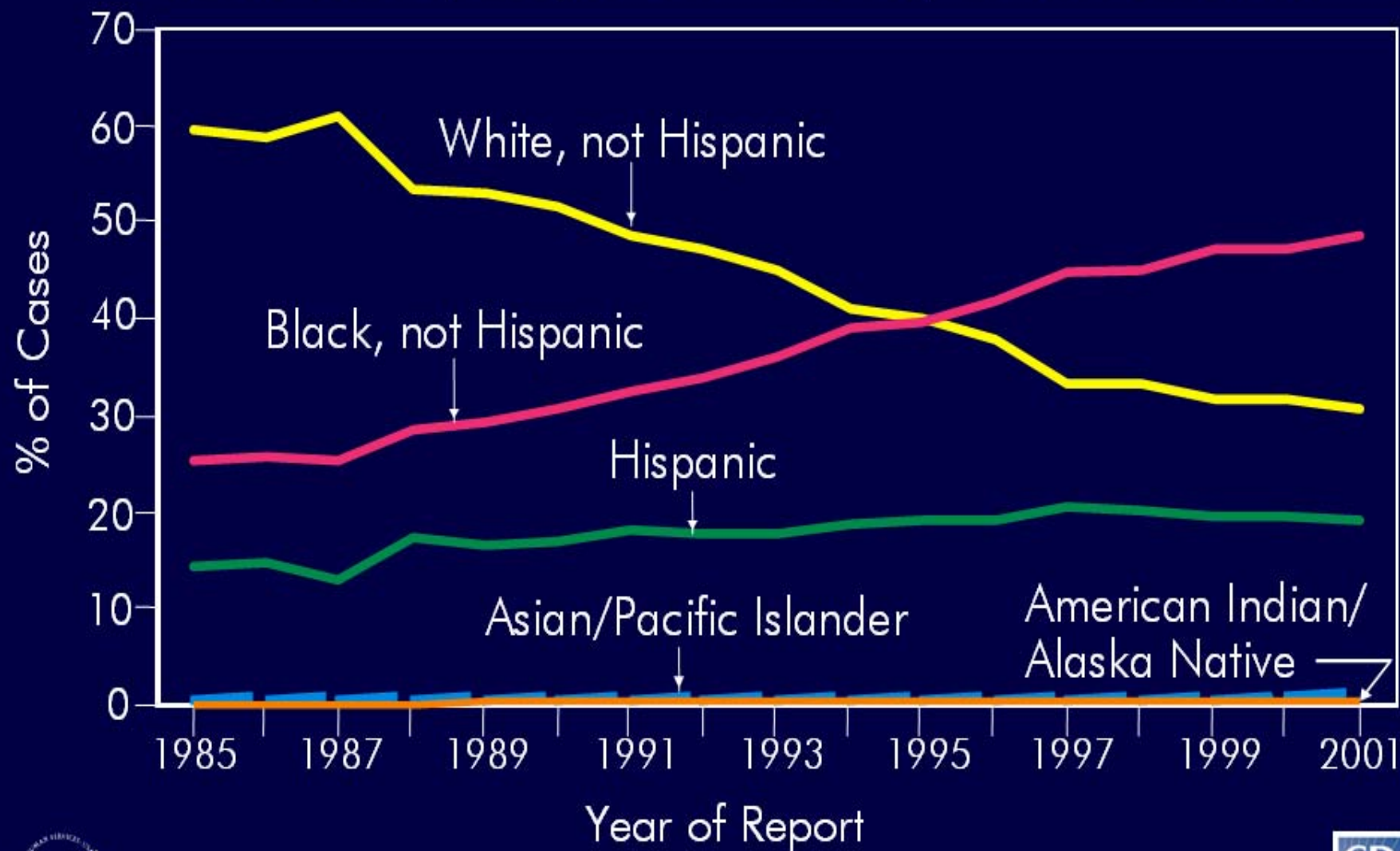


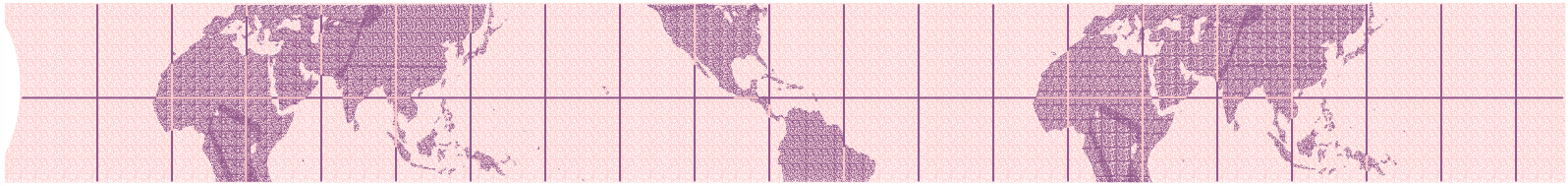
HIV/AIDS in South Africa: Age and Gender Distribution of HIV



Source: Abdool Karim Q, Abdool Karim SS, Singh B, Short R, Ngxongo S. Prevalence of HIV infection in Rural South Africa. AIDS 1992; 6: 1535 - 1539

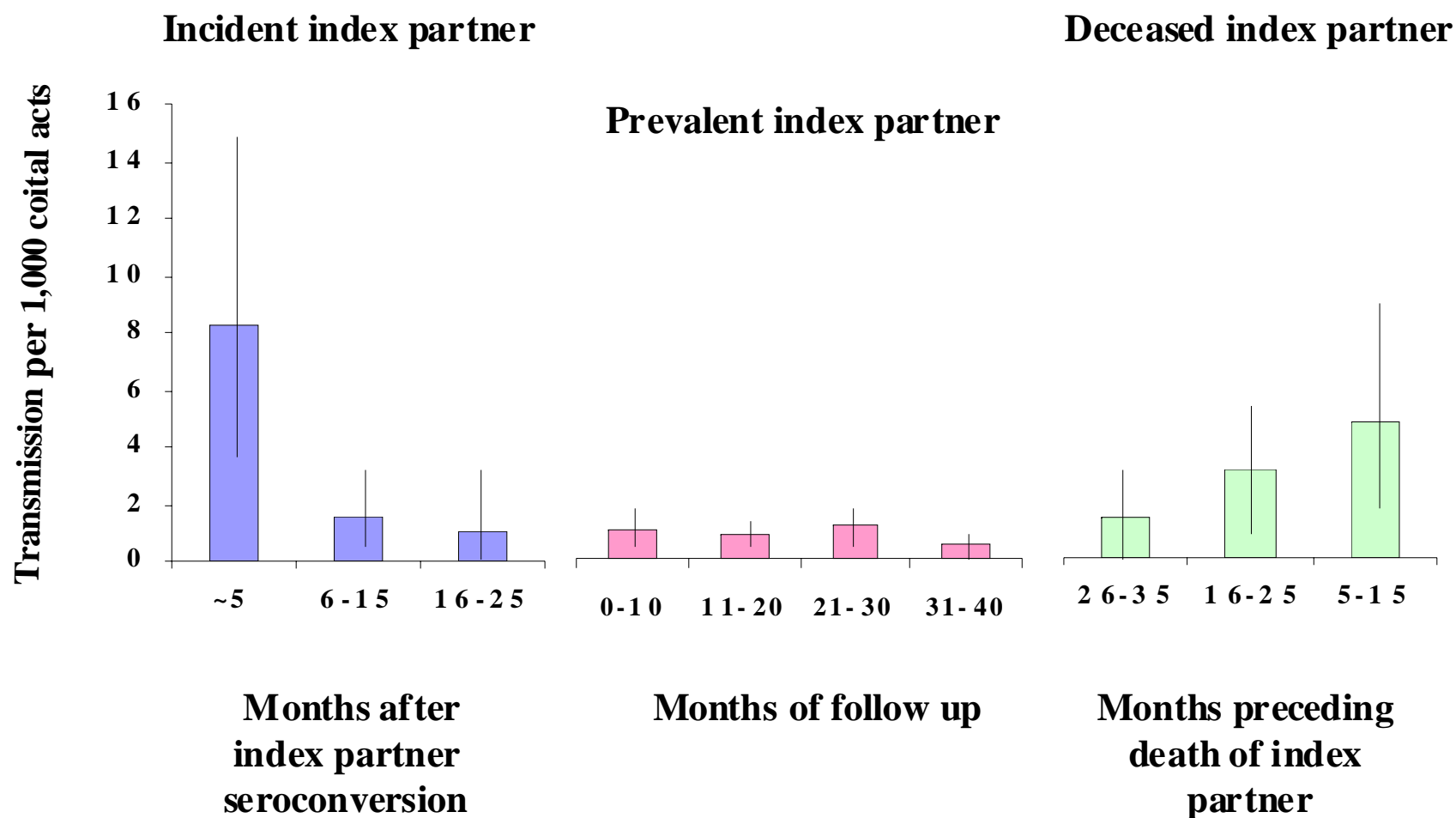
Proportions of AIDS Cases, by Race/Ethnicity and Year of Report, 1985 - 2001, United States

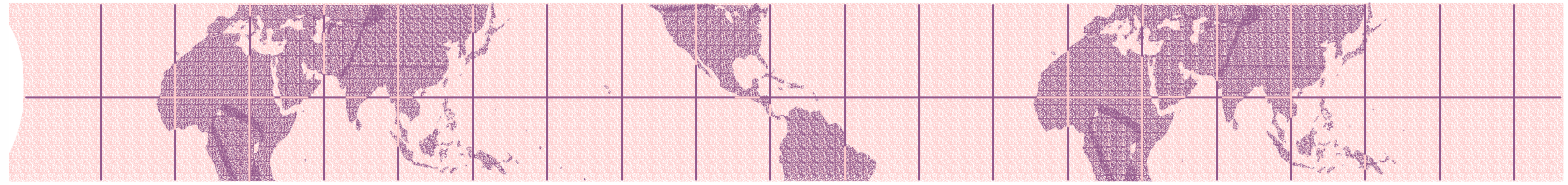




- **Trials underway to evaluate drugs to prevent HIV acquisition**
 - ART in discordant couples 2004 - 2009
 - ACV in HSV-2+ persons 2003 - 2007
 - Tenofovir PREP 2004 - 2007
- **Circumcision trials** 2003 - 2008
- **More VCT and ART available in developing countries?**
- **Better infrastructure?**

HIV Transmission is Driven by People in Early and Late Disease



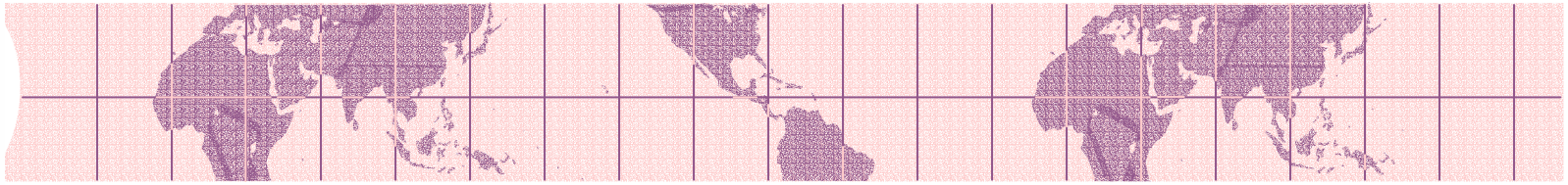


Prevention Research

➤ ART to prevent transmission

- ART or other therapeutic interventions in acute/early infection
 - Impact on transmission and disease progression; resistance; immune responses, etc.
- (ART in established infection)
- (PEP and PREP)
 - Safety, acquisition

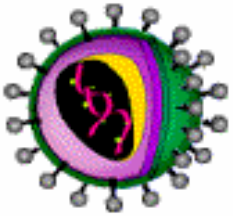
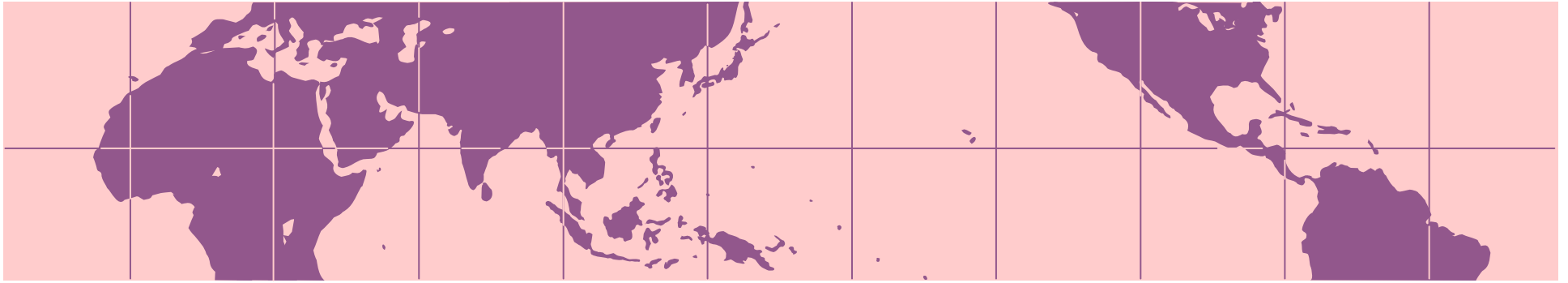




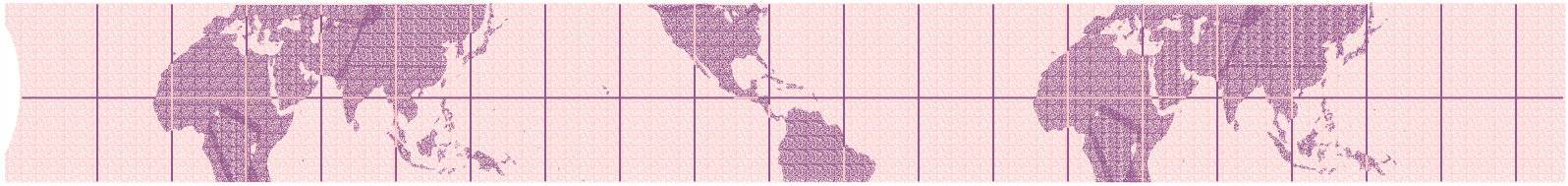
Prevention Research

- **Treatment or prevention of STDs (DMID, NIMH)**
 - Pharmacologic, vaccines, behavioral, surgical
- Behavior interventions to reduce HIV risk behaviors AND acquisition or transmission (NIMH)
 - Individual and/or community
 - VCT uptake; abstinence messages; ART availability; sex education
 - “Dosage”; “delivery”; “durability”
- Interventions to reduce HIV acquisition or transmission in drug users (NIDA)





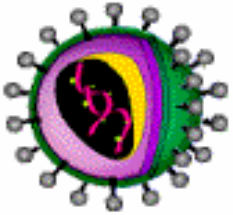
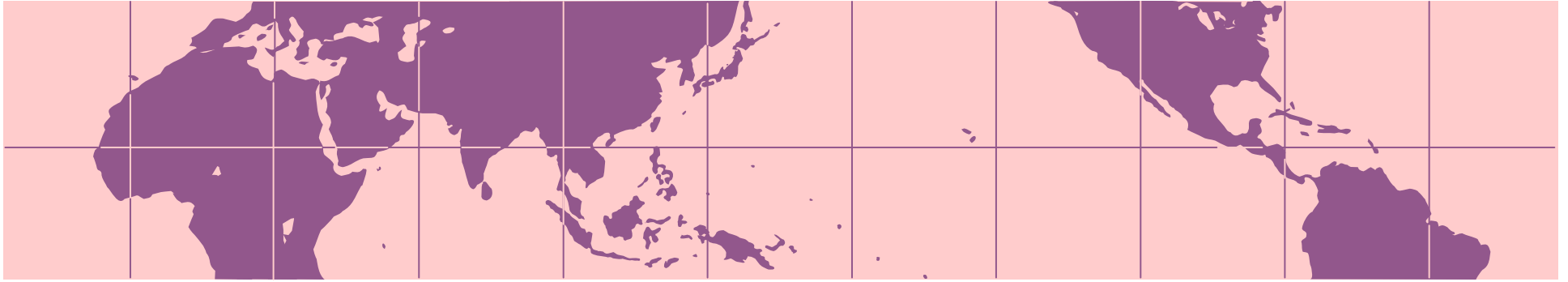
Questions?



MTCT Research: Objectives

- Identify safe, practical, and more effective approaches to further reduce MTCT, especially in resource-poor settings
- Define treatment options for both mother and child
- Provide technical knowledge to ensure prolonged success of MTCT programs





**Where do we think
prevention of MTCT will
be in 2006 – 2013?**

THE LANCET

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Volume 362

September 13, 2003

Intrapartum and Neonatal Single-Dose Nevirapine Compared with Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Kampala, Uganda: 18-Month Follow-Up of the HIVNET 012 Randomised Trial

J Brooks Jackson et al.



- **Studies of nevirapine to protect against breast milk transmission**
 - 6 weeks +/- HIVIG – results ~ 2005
 - 6 months – results ~ 2008
- **Information on occurrence and implications of resistance**
 - OCTANE trial completed
 - Results of short course post-partum trials
 - Comparison of ART combinations in NVP-exposed babies
- **More ART use in developing countries**
- **Additional vaccines ready for testing in infants**





Prevention of Mother-Child Transmission (and Impact on Future Treatment) (NICHHD)

➤ **Strategies to optimize and simplify regimens** (when mothers not on drug for their own disease)

- Decrease transmission, especially during breastfeeding period
- Minimize drug toxicity (esp high CD4 moms)
- Prevent drug resistance
- Evaluate impact of resistance on future treatment options
 - mothers, children, and communities
 - mothers' future pregnancies

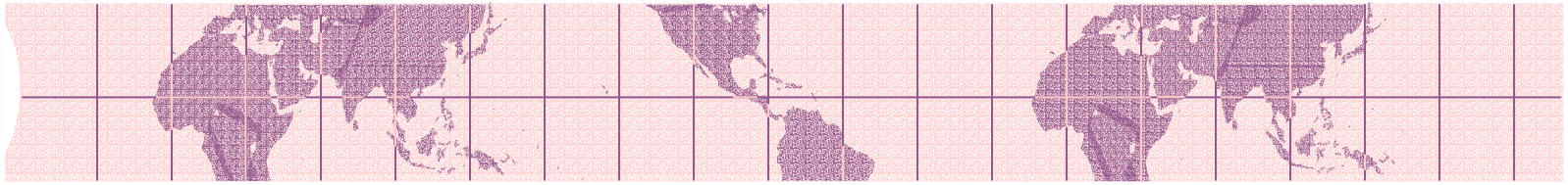




Prevention of Mother-Child Transmission (and Impact on Future Treatment) (NICHD)

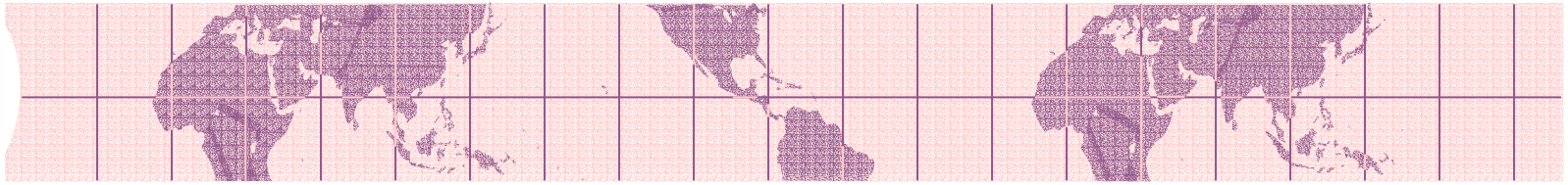
- **Strategies to optimize drug regimens pre-, peri- and post-partum** (when mothers on drug for their own disease)
 - Further decrease transmission rates
 - Prevent drug resistance
 - Minimize toxicities
 - Simplify delivery
 - Evaluate the development and impact of resistance on MTCT and future treatment options for mother and child





Prevention of Mother-Child Transmission (and Impact on Future Treatment) (NICHD)

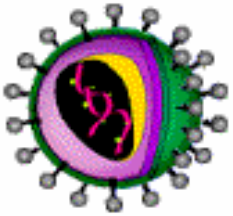
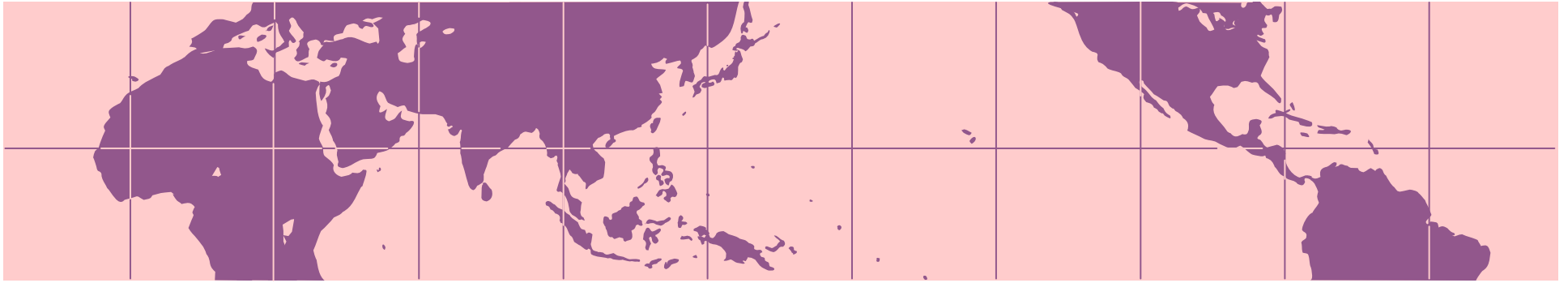
- **Evaluate safety and PK of new drugs,
drug combinations**
 - **HIV negative, non-pregnant women**
 - **HIV positive, non-pregnant women**
 - **HIV positive, pregnant women**
 - **HIV positive, very young children**



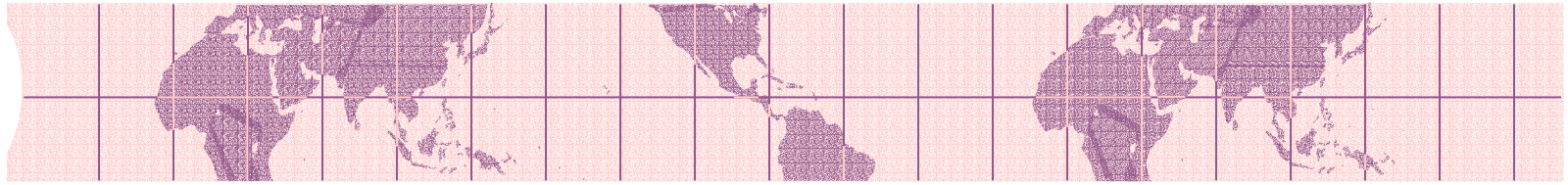
Prevention of Mother-Child Transmission (and Impact on Future Treatment) (NICHD)

- **Safety and efficacy of vaccines to prevent BF transmission**
- **Safety and efficacy of passive immunization of newborns**





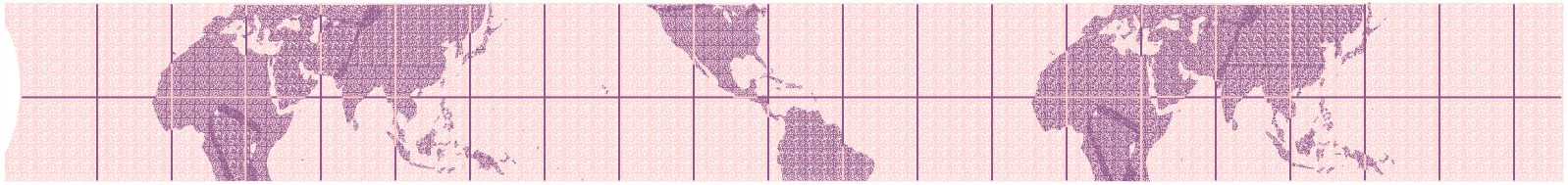
Questions?



Cross-Cutting Principles

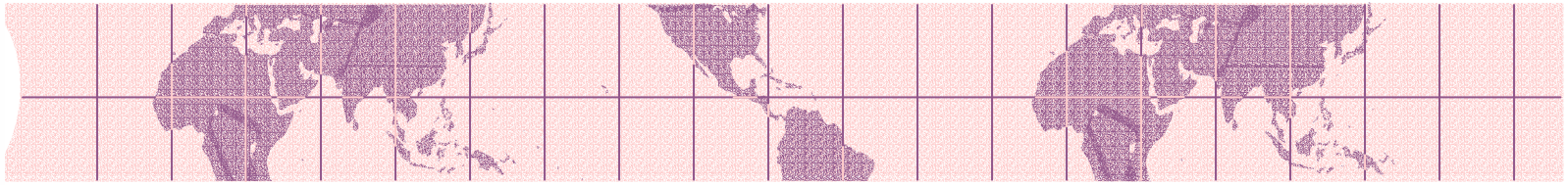
- Feed information on seroconverters in vaccine/prevention studies into acute infection data base or studies
- Identify highest risk populations to size and cost of vaccine and prevention efficacy trials (epi, incidence)
- Behavioral interventions in all studies (NIMH, NIDA)
- Role of host differences in outcomes (HLA/other genetics, age, gender...) (NICHD)
- Refer HIV+ during screening to treatment programs or research studies





Cross-Cutting Principles

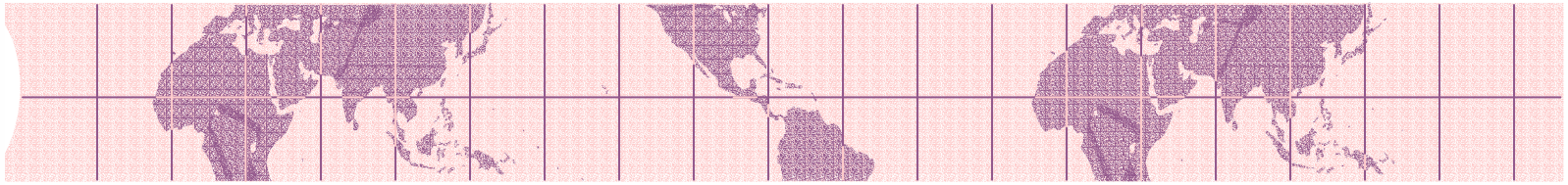
- **Role of host differences in outcomes (HLA/other genetics, age, gender...)
(NICHHD)**
- **Weigh development of mega-sites vs. many smaller sites**
- **Develop common laboratory and data management elements to help address important questions that cannot be studied by a single group**



Clinical Research: Populations and Communities

- Identify underserved or disenfranchised populations (e.g. women, minorities, adolescents, young children)
- Specify barriers to participation in clinical research for these and other special populations
- Develop strategies to address the problems identified above





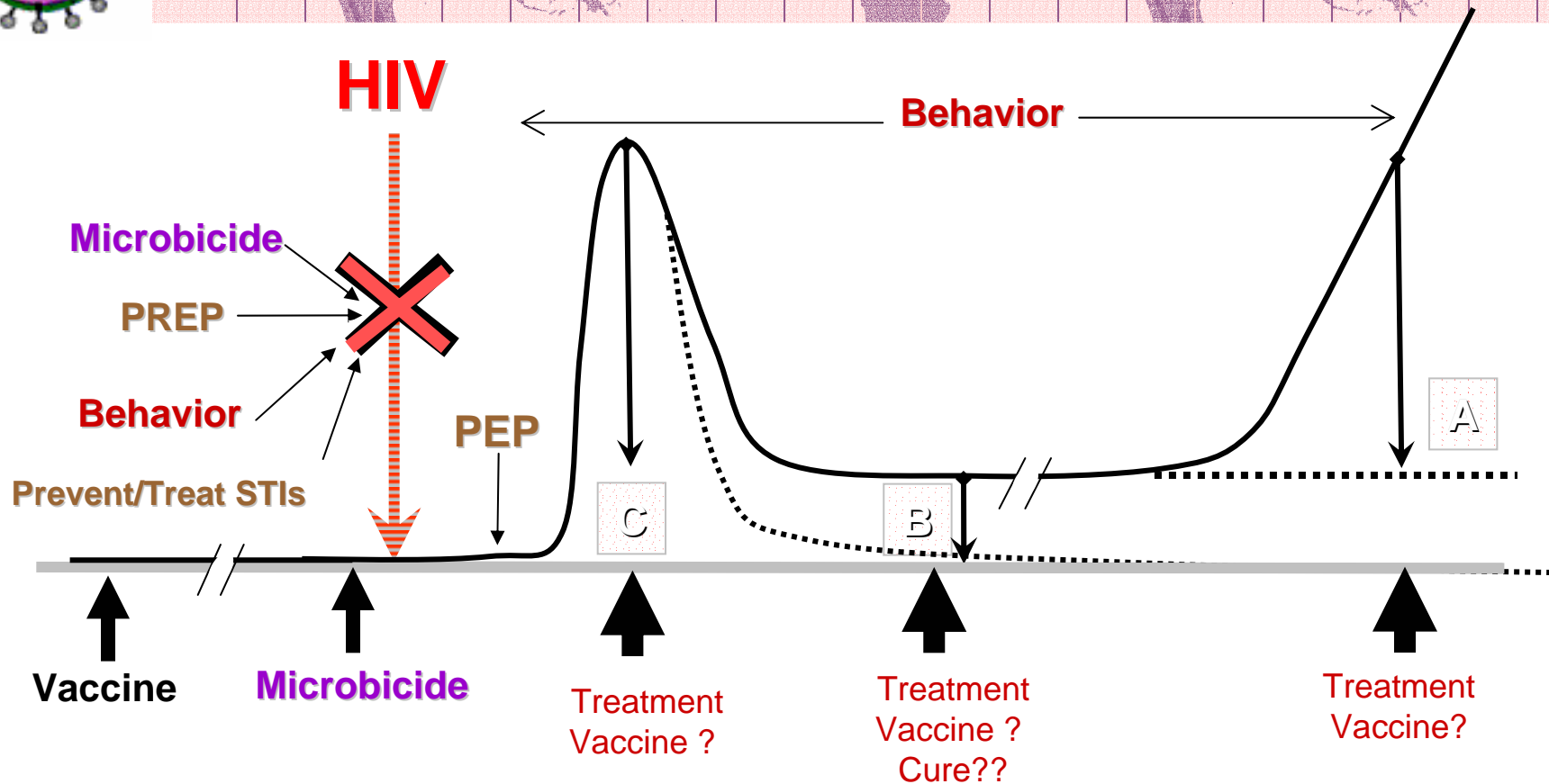
DAIDS Scientific Priorities

- Vaccine research and development
- Therapeutics - translational research/ drug development
- Therapeutics - optimization of clinical management
- Microbicide research and development
- Prevention of maternal-child transmission
- Prevention research





DAIDS Mission: Help Stop the HIV/AIDS Epidemic



Populations: Adults ←
Infants ↔
Children ←
Adolescents

- A.** Stop Progression, Development of Resistance
- B.** Lower Set Point or Eliminate HIV
- C.** Lower Initial Peak of Viremia



DHHS/NIH/DAIDS

ARAC 5-24-04





Leadership Groups RFA

**Translational
Research /
Drug
Development**

**Mother to Child
Transmission**

Microbicides

**Optimization of
Clinical
Management**

**HIV
Vaccines**

**Prevention of
HIV
Infection**

